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Genetics of Hyperparathyroidism Including Parathyroid Cancer

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SYNOPSIS

Primary hyperparathyroidism (HPT) is a metabolic disease caused by the excessive secretion of parathyroid hormone from one or more neoplastic parathyroid glands. HPT is largely sporadic, however it can be associated with a familial syndrome. The study of such families led to the discovery of tumor suppressor genes whose loss–of-function is now recognized to underlie the development of many sporadic parathyroid tumors. Heritable and acquired oncogenes causing parathyroid neoplasia are also known. Studies of somatic changes in parathyroid tumor DNA and investigation of kindreds with unexplained familial HPT promise to unmask more genes relevant to parathyroid neoplasia.

Keywords

tumor suppressor; oncogene; multiple endocrine neoplasia; MEN1; MEN2A; CDC73; CCND1; RET; CASR; CDKN1B

Introduction

Primary hyperparathyroidism (HPT) is a disorder of mineral metabolism, typically manifesting in hypercalcemia, that results from the excessive secretion of parathyroid hormone from one or more neoplastic parathyroid glands.[1] Although HPT is mostly sporadic, familial forms of HPT represent some 2 to 5% of total cases, the majority of which are caused by germline mutation of known HPT-susceptibility genes (Table 1). Investigation of the molecular genetics underlying these rare familial syndromes has yielded significant insight into the pathophysiology of both sporadic and familial parathyroid neoplasms. Signaling involving the G protein-coupled calcium-sensing receptor (CaSR) impacts the hormonal function of parathyroid cells, and the mutation of genes involved in CaSR signaling has also been implicated in familial syndromes of PTH-dependent hypercalcemia.

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This monograph will review our current knowledge of the genetics of HPT and PTH-dependent hypercalcemia due to benign and malignant parathyroid disease.

Pathophysiology of Primary Hyperparathyroidism

Maintenance of the serum calcium concentration within a relatively narrow physiologic range is achieved by regulation of parathyroid hormone (PTH) secretion from parathyroid cells in response to changes in the circulating ionized calcium level. The G protein-coupled CaSR located on the surface membrane of the parathyroid chief cells negatively regulates the secretion of PTH.[2,3] In clinical medicine, HPT is typically defined by the conjunction of elevated serum ionized calcium with inappropriately elevated PTH.[1] Most parathyroid tumors are benign adenomas. Parathyroid carcinoma is a rare cause of HPT seen in less than 1% of cases.

Approximately 2 to 5 % of cases of HPT are associated with familial disease. Study of this small subset has nevertheless provided great insight into the genetic changes and molecular pathways that promote parathyroid neoplasia (Table 1). The most common genetic disorders associated with HPT are MEN1, multiple endocrine neoplasia type 2A (MEN2A), HPT-JT, and familial isolated hyperparathyroidism (FIHP).[4–7] Familial hypocalciuric hypercalcemia (FHH) is a related, genetically heterogeneous, largely benign condition of PTH-dependent hypercalcemia often mimicking HPT that does not correct with partial or subtotal parathyroidectomy (PTX).[8] These genetic disorders and their relation to the underlying molecular and genetic alterations relevant to parathyroid neoplasia will be discussed in detail below.

Knudson’s Two-Hit Hypothesis and Tumor Suppressor Genes

Some forty-five years ago, Alfred Knudson proposed a model for tumor development based on his epidemiologic analysis of retinoblastoma.[9] Familial retinoblastoma is much more rare than sporadic retinoblastoma, yet the former has a much earlier age of onset and is more frequently binocular. According to the “two-hit” hypothesis of neoplasia proposed by Knudson, two events (or “hits”) in an affected cell confer a selective growth advantage and result in its clonal expansion.[10]

In accordance with clinical and molecular genetic data accrued since his original proposal, Knudson’s concept can be updated. In many hereditary tumor syndromes, an inherited mutation in the germline DNA affecting one allele of a tumor suppressor gene represents the first event or “hit” that is present in all the cells of the affected offspring (Fig. 1). The tendency for bilateral and/or multifocal disease in hereditary tumor syndromes as well as the earlier age of onset are explained by the greater likelihood of any particular cell acquiring a “second hit”, i.e. a somatic mutation in second allele of the same tumor suppressor gene. The “second hit”, that inactivates the remaining wild-type allele, most often results from large subchromosomal or even chromosomal deletion or else DNA rearrangement (Fig. 1). Bi-allelic inactivating mutation of the *MEN1* and the *CDC73/HRPT2* tumor suppressor genes can frequently be demonstrated in DNA derived from parathyroid tumors, in the context of the familial syndromes MEN1 and HPT-JT, respectively. In the majority of such

patients, a germline loss-of-function mutation of the associated tumor suppressor gene can be demonstrated, representing the first “hit” (Fig. 1).

Clinical Features and Genetics of Multiple Endocrine Neoplasia type 1

MEN1 is the most common familial cause of primary hyperparathyroidism.[11] MEN1 is characterized by a tendency to develop tumors in the anterior pituitary, parathyroid glands, and enteropancreatic endocrine cells, although tumors in several other endocrine organs and in non-endocrine tissues such as skin and smooth muscle can also be associated with the syndrome.[5,12] Some 10% of MEN1 is sporadic.

Familial MEN1 is inherited in an autosomal dominant fashion. Germline inactivation of one allele of the *MEN1* gene on chromosome 11q13 confers the tumor susceptibility.[13] More than 400 distinct germline mutations in *MEN1* have been described in patients and kindreds with MEN1. The vast majority of parathyroid and other syndromic tumors from MEN1 patients can be shown to harbor a somatic mutation or deletion of the second wild-type *MEN1* allele.[5,14]

Molecular genetic analysis of sporadic parathyroid adenomas using conventional DNA sequencing methods identified somatic *MEN1* mutation involving at least one allele with a frequency of 3–35%.[15–19] The frequency ranged from 26–37% in studies that looked at LOH at 11q13 in sporadic parathyroid adenomas. Studies of sporadic benign parathyroid tumor DNA employing whole exome sequencing (WES) methodology identified somatic *MEN1* mutation in some 35% of tumors, similar to results using conventional DNA sequencing methods.[20,21] Since HPT is most penetrant feature of MEN1 and is usually its initial manifestation, *bona fide* MEN1 kindreds may rarely be misassigned a provisional diagnosis of FIHP if only younger mutation carriers are evaluated at the time of initial family ascertainment.

The association of *MEN1* mutation with parathyroid carcinoma is rare. At least two cases of parathyroid cancer have been reported in patients with MEN1, one with associated parathyroid adenoma, and the other with bilateral parathyroid carcinoma.[22,23]

Clinical Features and Genetics of the Hyperparathyroidism-Jaw Tumor Syndrome

HPT-JT is a rare autosomal dominant familial cancer syndrome of variable and incomplete penetrance manifested by HPT, cemento-ossifying tumors of the maxilla and mandible, and less commonly uterine tumors and/or renal cysts.[24–26] HPT is the most penetrant feature and usually the presenting manifestation. In contrast to MEN1, parathyroid carcinoma is frequent in HPT-JT, affecting some 20% or more of those with HPT.[24–27] Approximately 10% of obligate or genetically confirmed carriers have no clinical manifestations.

A loss-of-function mutation of *CDC73/HRPT2* can be demonstrated in the germline of a majority of HPT-JT kindreds.[28] Most such *CDC73/HRPT2* mutations are predicted to inactivate gene function via frameshift or nonsense mutation.[29] Patients with germline

deletion of the *CDC73/HRPT2* gene have also been reported.[30–32] The *CDC73/HRPT2* gene encodes the protein parafibromin.[28] Parafibromin is a presumed tumor suppressor protein because germline-inactivating mutation of the *CDC73/HRPT2* gene predisposes to the full or partial expression of HPT-JT. Somatic mutation of *CDC73/HRPT2* is uncommon in sporadic parathyroid adenomas.[33] In contrast, mutations of *CDC73/HRPT2* are frequently seen in apparently sporadic cases of parathyroid carcinoma.[34–36] Interestingly, exome sequence analysis of tumor DNA from parathyroid carcinoma revealed preferential amplification of the mutant *CDC73/HRPT2* allele.[37] Some 25% of patients with apparently sporadic parathyroid cancer may harbor germline *CDC73/HRPT2* mutations, suggesting that such cases may represent undiagnosed or incompletely penetrant HPT-JT.[36,38] Besides HPT-JT kindreds, a subset of patients with the FIHP phenotype also harbor germline mutation of *CDC73/HRPT2*, indicating this familial disorder may represent an incomplete expression of HPT-JT.

Clinical Features and Genetics of Multiple Endocrine Neoplasia Type 4

Multiple Endocrine Neoplasia Type 4 (MEN4, sometimes called MENX) is a syndrome originally described by Pellegata *et al* in a multi-generational family with MEN1-like features, including a proband with acromegaly and HPT but lacking *MEN1* mutation.[39] Several members of this kindred, including the proband, were shown to harbor a germline heterozygous nonsense mutation in *CDKN1B*, encoding the cyclin dependent-kinase inhibitor p27(Kip1).[39] Investigation of this locus followed from the genetic analysis of rats with the MenX phenotype, a recessively inherited condition characterized by the development of bilateral pheochromocytomas, paragangliomas, parathyroid adenomas and thyroid C cell hyperplasia.[39,40] Only a single member of the MEN4/MENX kindred described by Pellegata *et al* manifested HPT (the proband).[39]

Since the original report by Pellegata and co-workers,[39] several groups have investigated a role for mutation of *CDKN1B* in parathyroid neoplasia. Apart from the demonstration of HPT linked to *CDKN1B* mutation in monozygotic twins,[41] none of the studies of *CDKN1B* mutation-positive kindreds expressing MEN1-like tumors but lacking *MEN1* germline mutation, and thus characterized by the MEN4 designation, has identified kindreds that include more than one genetically unique member with HPT proven to segregate with germline *CDKN1B* mutation.[39,41–46] At least one study of patients with features of genetic predisposition to HPT failed to identify any cases with germline *CDKN1B* mutation.[18] On the other hand, non-familial presentation of primary HPT due to parathyroid adenomas in association with somatic and germline mutation of *CDKN1B* has been documented.[47]

The characterization of *CDKN1B* as a low-penetrance susceptibility gene for the development of primary parathyroid tumors is supported by good evidence.[47,48] As such, *CDKN1B* remains a reasonable hypothetical candidate for which germline mutation may provide an etiology for some cases of familial HPT. More research will be required, however, to justify including germline inactivating mutation of *CDKN1B*, associated with MEN4, in the differential diagnosis of familial HPT. At a minimum such justification would seem to require identification and characterization of at least one family that includes more

than one genetically unique member with HPT linked to pathologic mutation of *CDKN1B* in the germline.

Clinical Features and Genetics of Familial Isolated Hyperparathyroidism

FIHP is a genetically heterogeneous, non-syndromic, clinically defined diagnosis of exclusion in kindreds with two or more cases of HPT but lacking the specific features of MEN1, MEN2A, HPT-JT or FHH. While germline mutation of *MEN1*, *CDC73/HRPT2* or *CASR* may account for a minority of kindreds with the FIHP phenotype upon initial ascertainment,[7,49–51] the majority of FIHP kindreds lack mutations in these known HPT-susceptibility genes.[7,49] A distinct genetic etiology resulting in the FIHP phenotype has not yet been defined, although a genome-wide screen of seven FIHP families has identified a 1.7 Mb region of suggestive linkage on the short arm of chromosome 2, at location 2p14-p13.3.[52]

Clinical Features and Genetics of Familial Hypocalciuric Hypercalcemia

FHH is a genetically heterogeneous, clinically benign condition of PTH-dependent hypercalcemia often mimicking HPT (Table 1).[8] FHH cases almost always remain hypercalcemic following partial or subtotal PTX. FHH is a transmitted in an autosomal dominant fashion and usually causes mild HPT with relative hypocalciuria; hypercalcemia in FHH is highly penetrant at all ages, even in the perinatal period.[8] Most cases of FHH are type 1 (FHH1) and result from heterozygous loss of function mutation of the *CASR* gene on chromosome 3 that encodes the CaSR.[2,3,53–56] The homozygous or compound heterozygous inheritance of two inactive *CASR* alleles typically results in the phenotype of neonatal severe hyperparathyroidism (NSHPT).[54–56] The non-neoplastic nature of the abnormal parathyroids associated with germline *CASR* loss-of-function mutation was underscored by a recent molecular genetic analysis of enlarged parathyroid glands from a patient with NSHPT that demonstrated generalized polyclonal hyperplasia, rather than the monoclonality that would be expected in *bona fide* parathyroid tumors.[57]

Somatic inactivation of *CASR* has not been found in sporadic parathyroid tumors studied to date,[58,59] even though significant loss of *CASR* expression, not due to allelic loss, has been documented in parathyroid adenomas and very likely contributes to their altered calcium set point for PTH release.[60]

Type 2 FHH (FHH2) due to germline loss-of-function mutation of *GNA11*, encoding the G protein α11 subunit[61,62], and type 3 FHH (FHH3) due to germline loss-of-function mutation in *AP2S1*, encoding the adaptor protein-2 sigma subunit involved in clathrin-mediated endocytosis,[63–66] have been recently described. Somatic mutation of neither *GNA11* nor *AP2S1* has been reported in sporadic parathyroid tumors.

Oncogenes and Proto-Oncogenes

Oncogenes derive from naturally occurring genes, referred to as proto-oncogenes, which positively regulate cell division and/or cell growth.[67] Oncogenes represent mutationally activated or overexpressed forms of proto-oncogenes that can induce tumor formation, often

in a tissue-specific fashion. Proto-oncogenes frequently encode proteins that are involved in signal transduction, particularly in pathways mediating mitogenic signals. Among the etiologies of currently recognized familial cancer syndromes, germline mutational activation of proto-oncogenes is quite rare compared to the germline inactivation of tumor suppressor genes. This is presumably because of the disruptive effect constitutive proliferative signalling created by the activation of most proto-oncogenes would likely have on embryonic and fetal development.

Clinical Features and Genetics of Multiple Endocrine Neoplasia Type 2A

Classical multiple endocrine neoplasia type 2A (MEN2A) is a familial syndrome characterized by medullary thyroid cancer (MTC), pheochromocytoma, and primary HPT. HPT in MEN2A resembles sporadic HPT in its clinical presentation, is usually mild, and is almost always due to benign parathyroid tumors. MEN2A is transmitted in an autosomal dominant fashion. MEN2A is caused by germline gain-of-function mutation in the *RET* (REarranged during Transfection) proto-oncogene. *RET* encodes a transmembrane receptor tyrosine kinase which, in conjunction with glial derived neurotrophic factor (GDNF)-family α co-receptors, binds GDNF family ligands.[68]

Germline gain-of-function mutations of *RET* are associated with three different endocrine tumor syndromes, all associated with MTC: MEN2A, multiple endocrine neoplasia type 2B (MEN2B), and familial medullary thyroid cancer (FMTC). Parathyroid tumors and HPT are not part of the MEN2B or FMTC disease pattern. Different germline *RET* mutations can result in the different disease phenotypes. In 95% of patients, MEN2A is associated with germline missense mutations that map to the receptor tyrosine kinase's extracellular cysteine-rich domain, involving *RET* codons 609, 611, 618, or 620 of exon 10 or codon 634 of exon 11.[69] About 85% of cases of MEN2A result from missense mutation of the cysteine residue present at codon 634.[70]

The Role of the *CCND1* Oncogene in the Pathophysiology of Parathyroid Tumors

The *CCND1* (or *PRAD1*, for parathyroid adenomatosis 1) oncogene was discovered during the molecular genetic analysis of several large sporadic parathyroid adenomas that harbored DNA re-arrangements involving the PTH gene locus on chromosome 11.[71–73] The *CCND1/PRAD1* oncogene in sporadic parathyroid tumors was identified downstream of a breakpoint caused by the pericentromeric inversion of chromosome 11 DNA.[73] The chromosomal inversion positions the 5′ PTH gene regulatory region (normally located at 11p15) just upstream of the *CCND1/PRAD1* proto-oncogene resident at 11q13.[71–73] The product encoded by the proto-oncogene was subsequently recognized to be a member of the cyclin family based on sequence homology[73] and the gene was re-named cyclin D1 (*CCND1*). It was subsequently shown that transgenic overexpression of *CCND1* in the parathyroid tissue of mice causes cell proliferation and recapitulates the metabolic abnormalities typical of HPT in humans.[74]

CCND1 is overexpressed in some 20 to 40% of sporadic benign parathyroid tumors and in an even higher percentage of parathyroid cancers.[75–78] Activating missense mutations in the CCND1 coding region have not been observed in sporadic parathyroid adenomas.[79] No somatic chromosomal rearrangements involving *CCND1* have been reported in parathyroid carcinoma. Neither germline activating missense mutations nor germline chromosomal translocations/rearrangements involving *CCND1* have been identified in any familial form of HPT.

The Role of Other Oncogenes in the Pathophysiology of Parathyroid Tumors

Analysis of eight sporadic parathyroid adenomas by WES and the subsequent targeted sequencing of DNA from an additional 185 parathyroid adenomas demonstrated the Y641N missense mutation in *EZH2* (*enhancer of zeste 2*) in two out of 193 independent parathyroid tumors.[20] *EZH2* encodes the catalytic subunit of polycomb repressive complex 2 and somatic mutations of EZH2 residue Y641, including Y641N, had previously been reported in certain categories of lymphoma.[80] Mutational analysis of a subsequent set of 80 sporadic benign and malignant parathyroid tumors by an independent group did not find any pathogenic *EZH2* variants however, suggesting such somatic mutation may be rare.[81] In the context of lymphoma, *EZH2* is thought to function as a proto-oncogene.[80] Since *EZH2* Y641N mutation and gene overexpression have been reported in parathyroid tumors, *EZH2* may be considered a candidate proto-oncogene in the parathyroid context, also, if further investigation confirms these initial observations. No transgenic mouse models targeting *EZH2* mutation or overexpression to parathyroid tissue have yet been reported.

Somatic mutations in the candidate parathyroid proto-oncogene *ZFX*, a member of the Krüppel associated box domain-containing zinc finger protein transcription factors, were first identified by WES analysis of DNA extracted from 19 parathyroid adenomas and matched germline DNA, with confirmation by direct sequencing of tumor DNA from an additional 111 parathyroid adenomas.[82] Several lines of evidence suggest that the somatically acquired mutant *ZFX* alleles detected in parathyroid tumors may act as oncogenes.[83] Development of a transgenic mouse model targeting mutant ZFX protein expression to parathyroid tissue and/or *in vitro* functional characterization of the mutant ZFX protein will help to clarify the potential significance of *ZFX* as a parathyroid proto-oncogene.

Future Considerations

It is quite likely that the dysregulation of other genes, besides those discussed above, predispose to parathyroid neoplasia. As previously noted, the susceptibility to parathyroid neoplasia in the majority of FIHP kindreds appears to result from the germline mutation of genes not currently recognized for a role in parathyroid disease: 53 among 76 families initially considered as FIHP in 5 clinical studies that investigated for germline *MEN1*, *CASR* and *CDC73/HRPT2* gene mutation, or nearly 70%, had no currently recognized syndromic etiology.[7,49–51]

The existence of currently unidentified parathyroid tumor suppressors and oncogenes is also suggested by the analysis of parathyroid tumors for the loss or gain of specific regions of chromosomal DNA using techniques such as comparative genomic hybridization (CGH). Several investigators have found recurrent loss of chromosomal DNA at the 1p, 6q, 9p, and 13q loci in parathyroid tumors indicating the potential presence there of novel parathyroid tumor suppressor genes.[84–87] The possible presence of novel oncogenes at 9q, 16p, 19p, and Xq is suggested by a convergence of results from several laboratories that demonstrate specific chromosomal gain at these loci in benign or malignant parathyroid tumors.[84,86–88]

WES analysis of benign and malignant parathyroid tumors shows great promise for the identification of somatic and germline gene mutations predisposing to parathyroid neoplasia. The success of this method in the identification of the candidate parathyroid oncogenes *EXH2*[20] and *ZFX*[82] has been discussed above. Similarly exome sequence analysis of DNA from parathyroid carcinomas has highlighted the potential significance of recurrent germline and somatic inactivating mutations of *PRUNE2* in this context.[37] The sensitivity and comprehensive quality of WES and other emerging next generation sequencing modalities will undoubtedly accelerate our understanding of the pathophysiology of familial and sporadic parathyroid neoplasia in the years ahead.

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Key Points

- Primary hyperparathyroidism, due to parathyroid tumors, is mostly sporadic.
- The molecular genetic investigation of rare syndromic forms of hyperparathyroidism has nevertheless led to significant advances in our understanding of both familial and sporadic parathyroid neoplasia.
- Both oncogenes and tumor suppressors have been implicated in the etiology of parathyroid tumors.
- The discovery of novel parathyroid tumor susceptibility genes will likely result from the application of next generation sequencing methods to the analysis of sporadic parathyroid tumors and non-syndromic familial cases of hyperparathyroidism.

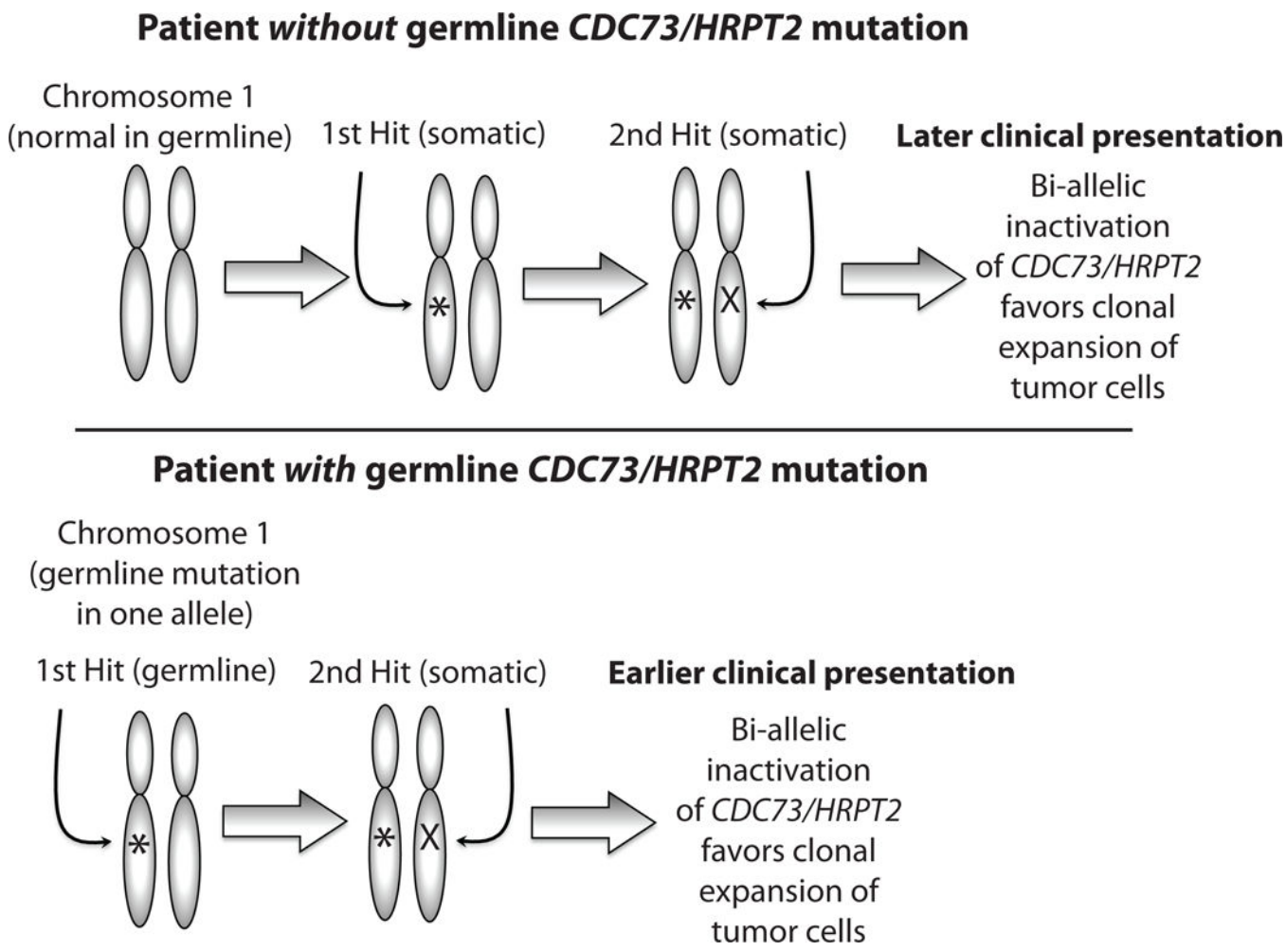

Figure 1. Two-hit loss of function mutation of the *CDC73/HRPT2* tumor suppressor in parathyroid neoplasia

Benign or malignant parathyroid tumors causing hyperparathyroidism (HPT) can result from two-hit loss of function of the *CDC73/HRPT2* tumor suppressor gene according to the Knudson hypothesis (see text). The human *CDC73/HRPT2* gene is on chromosome 1 at location 1q25. Upper: In a patient without germline *CDC73/HRPT2* mutation, both alleles of *CDC73/HRPT2* are initially normal in all parathyroid cells. Subsequent step-wise acquired or somatic inactivation of both alleles in the same parathyroid cell results in clonal expansion that may lead to a sporadic parathyroid tumor. Lower: In a patient with germline *CDC73/HRPT2* mutation in one allele, an acquired or somatic DNA mutation at the *CDC73/HRPT2* locus of the remaining allele in a parathyroid cell results clonal expansion of that cell that may lead to a benign or malignant parathyroid tumor. Patients with germline *CDC73/HRPT2* mutation who develop parathyroid adenomas or cancer can present sporadically (if lacking or unaware of relevant family medical history), or belong to a kindred with familial isolated HPT or the hyperparathyroidism-jaw tumor syndrome (HPT-JT). The presence of the first germline mutation at birth in all parathyroid tissue accelerates

the acquisition of two hits within a single parathyroid cell and accounts for the earlier age of disease presentation typical of familial forms of HPT such as HPT-JT.

Table 1

Genes implicated in syndromic and sporadic parathyroid tumorigenesis, and related syndromes

Gene	Protein encoded	Associated hyperparathyroid syndrome: main syndromic manifestations	Features of syndromic parathyroid tumors	Defect in sporadic parathyroid tumors
MEN1	Menin	Multiple endocrine neoplasia type 1 (MEN1): anterior pituitary, parathyroid, enteropancreatic, foregut carcinoid tumors	Multiple, asymmetric tumors typical (> 99% benign)	Inactivation in ~25–35% of benign tumors; mutation exceedingly rare in cancer
CDC73/HRPT2	Parafibromin	Hyperparathyroidism-jaw tumor syndrome: fibro-osseous jaw, parathyroid, uterine tumors; renal cysts	Single tumor common (~15% malignant)	Inactivation in ~70% of cancers; mutation rare in sporadic adenomas
CDKN1B	P27(Kip1)	Multiple endocrine neoplasia type 4 (MEN4): anterior pituitary, other involvement varies	Single to multiple glands (benign in reports to date); can be recurrent	Loss-of-function mutation in ~5% of sporadic adenomas; including germline mutation in sporadic presentation
CASR	Calcium-sensing receptor	Familial hypocalciuric hypercalcemia type 1 (FHH1) with heterozygous inactivation; neonatal severe hyperparathyroidism (NSHPT) with homozygous inactivation	FHH1: near-normal size and surgical pathology; altered serum calcium set-point for PTH release NSHPT: Marked enlargement of multiple glands by polyclonal (non-neoplastic) mechanism	Decreased expression common; mutation exceedingly rare
GNA11	G protein subunit α11	Familial hypocalciuric hypercalcemia type 2 (FHH2)	ND	ND
AP2S1	adaptor protein-2 sigma subunit	Familial hypocalciuric hypercalcemia type 3 (FHH3): hypercalcemia more severe than in FHH1	ND	ND
RET	c-Ret	Multiple endocrine neoplasia type 2A: medullary thyroid cancer, pheochromocytoma, parathyroid tumors	Single tumor common (> 99% benign)	Mutation exceedingly rare
CCND1/PRAD1	Cyclin D1	NA	NA	Overexpression results from DNA rearrangement involving PTH gene

NA, not applicable

ND, not determined due to lack of relevant published studies