Genetics of Hyperparathyroidism, Including Parathyroid Cancer

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KEYWORDS

• Tumor suppressor • Oncogene • Multiple endocrine neoplasia • MEN1 • MEN2A • CDC73 • CCND1 • RET

KEY POINTS

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

INTRODUCTION

Primary hyperparathyroidism (HPT) is a disorder of mineral metabolism, typically manifesting in hypercalcemia, that results from the excessive secretion of parathyroid hormone from 1 or more neoplastic parathyroid glands.[1] Although HPT is mostly sporadic, familial forms of HPT represent some 2% to 5% of total cases, most 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

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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	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	HPT–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)	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	FHH1 with heterozygous inactivation; 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 (nonneoplastic) mechanism	Decreased expression common; mutation exceedingly rare
GNA11	G protein α11 subunit	FHH2	ND	ND
AP2S1	Adaptor protein-2 sigma subunit	FHH3: hypercalcemia more severe than in FHH1	ND	ND
RET	c-Ret	MEN2A: 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

Abbreviations: MEN1, multiple endocrine neoplasia type 1; MEN4, multiple endocrine neoplasia type 4; NA, not applicable; ND, not determined (lack of relevant published studies); NSHPT, neonatal severe hyperparathyroidism; PTH, parathyroid hormone.