Familial disorders of parathyroid glands

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Abstract

The molecular mechanisms underlying familial parathyroid diseases continue to be elucidated. The mechanisms of familial parathyroid diseases are better understood than many sporadic parathyroid diseases. Familial parathyroid disease is associated with multiple endocrine neoplasia type 1 which is associated with *MEN1* mutation, multiple endocrine neoplasia type 2A caused by *RET* mutation, and multiple endocrine neoplasia type 4 is caused with *CDKN1B* mutation. Sporadic parathyroid tumours are identified with mutations of *MEN1* but generally not of *RET*. *CDKN1B* mutations are also identified in sporadic forms of primary hyperparathyroidism, although very rarely. Calcium sensing receptor gene mutations are involved in familial hyperparathyroidism and hypoparathyroidism, but are generally not identified in sporadic parathyroid tumours. However, the *HPRT2* (*CDC73*) gene, which is mutated in hyperparathyroidism jaw-tumour syndrome and a subset of cases of familial isolated hyperparathyroidism, is frequently mutated in sporadic parathyroid carcinomas. Germline activating *GCM2* mutations were recently found associated with a subset of familial isolated hyperparathyroidism. Parafibromin, a protein encoded by *HPRT2*, has been used in the diagnostic setting. The understanding and pathogenesis of parathyroid disease continues to evolve.

Keywords adenoma; carcinoma; familial hyperparathyroidism; hyperparathyroidism; hyperplasia; hypoparathyroidism; multiple endocrine neoplasia; parathyroid

Introduction

The molecular mechanisms for familial parathyroid diseases are better understood than those of sporadic parathyroid lesions. Familial parathyroid disease is associated with multiple endocrine neoplasia type 1 (MEN1) which caused by germline mutation in the *MEN1* gene results in truncation of menin, the protein it encodes, while multiple endocrine neoplasia type 2A (MEN2A) caused by *RET* germline mutation. Recently, mutations of *CDKN1B*, originally described in rats, have been identified in humans with MEN1-like syndrome but without MEN1 mutation. *CDKN1B* encodes the cyclin dependent kinase inhibitor p27. Mutations in the calcium sensing receptor (*CASR*) gene are involved in familial hyperparathyroidism and hypoparathyroidism. Mutations in the *HPRT2* gene which encodes parafibromin are associated with hyperparathyroidism jaw-tumour syndrome and some cases of familial isolated hyperparathyroidism. Recently *GCM2* mutations were identified in a subset of cases of familial isolated hyperparathyroidism. Familial causes of hypoparathyroidism include velocardiofacial syndrome, Kenny-Caffey syndrome, *PTH* and *PTH receptor* mutations, among others as well as disorders of pseudohypoparathyroidism. Although the pathogenesis of familial parathyroid disease provides insight into the pathogenesis of some sporadic parathyroid diseases, the mechanisms regulating tumour development continue to be elucidated.

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Hyperparathyroidism

Primary hyperparathyroidism usually occurs sporadically, often in the fifth decade but can occur over a wide age range, and is more common in women. Parathyroid hormone is increased resulting in increased serum calcium. Historically, patients more often presented with symptoms such as nephrocalcinosis and osteopenia than today where many are asymptomatic with elevated serum calcium identified by screening or with mild symptoms such as weakness. The utilization of screening serum calcium in the early 1970s is associated with an increase in the incidence of primary hyperparathyroidism. Although most cases of hyperparathyroidism occur sporadically, hyperparathyroidism can be hereditary and/or associated with syndromes such as multiple endocrine neoplasia (MEN) type 1, MEN2A, MEN4, familial hypocalciuric hypercalcaemia, neonatal severe primary hyperparathyroidism, hyperparathyroidism-jaw tumour syndrome, and familial isolated hyperparathyroidism (Table 1).

Multiple endocrine neoplasia type 1 (MEN1)

Multiglandular parathyroid disease is the most common manifestation of MEN1, although single gland disease (parathyroid adenoma) and carcinomas can occur. Hyperparathyroidism associated with MEN1 occurs decades earlier than sporadic disease and males and females are affected equally, but patients with MEN1 may have their disease discovered earlier than those with sporadic or non-syndromic disease. Parathyroid disease is identified in approximately 90–95% of patients with MEN1, and approximately 20% of patients with primary parathyroid hyperplasia have MEN1. In multiglandular disease the parathyroid glands in MEN1 are often asymmetrically enlarged with increased numbers of chief cells with a nodular or a diffuse pattern. Parathyroid adenomas or single gland disease in MEN1 appears similar to sporadic parathyroid adenomas. In addition to parathyroid disease, MEN1 is associated with entero-pancreatic neuroendocrine tumours, pituitary adenomas, adrenocortical tumours, neuroendocrine tumours of the stomach, thymus, and lung, meningiomas, and cutaneous tumours (lipomas, angiofibromas, collagenomas).[1,2]

MEN1 occurs in a familial setting as an autosomal dominant disorder with high penetrance caused by germline *MEN1* mutation, with sporadic cases occurring from new mutations. *MEN1* (11q13) is a tumour suppressor gene that encodes menin, which is which is usually truncated but can absent or truncated with most germline or somatic MEN1 mutations of which over 1300 different mutations have been reported.[3,4] Germline *MEN1* mutations are identified in 80–94% of patients with familial MEN1 and 65–88% of patients with sporadic MEN1.[1,5] *MEN1* mutation detection rate increases with the number of MEN1 related tumours and family history of MEN1 as well as in patients with both parathyroid and pancreatic neuroendocrine tumours.[6,7]

Parathyroid disorders with associated genetic findings

Disorder	Genetics
Multiple endocrine neoplasia type 1	*MEN1* mutation (11q13) (AD)
Multiple endocrine neoplasia type 2A	*RET* mutation (10q21) (AD)
Multiple endocrine neoplasia type 4	*CDKN1B* mutation (12p13) (AD)
Familial hypocalciuric hypercalcaemia type 1	Heterozygous inactivating *CASR* mutation (3q13.3-q21)
Familial hypocalciuric hypercalcaemia type 2	*GNA11* mutation (19p13.3) (AD)
Familial hypocalciuric hypercalcaemia type 3	*AP2S1* mutation (19q13.3) (AD)
Some neonatal hyperparathyroidism	Heterozygous inactivating *CASR* mutation (3q13.3-q21)
Neonatal severe hyperparathyroidism	Homozygous or compound heterozygous inactivating *CASR* mutation (3q13.3-q21) (AR, AD)
Hyperparathyroidism jaw-tumour	*HRPT2* mutation (1q21-q31) (AD)
Familial isolated hyperparathyroidism	Unknown, possible variant MEN1/ HP-JT, *HRPT2* (*CDC73*) mutation, *GCM2* mutation (AD)
Autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED)	*AIRE* (autoimmune regulator) (21q22.3) mutation Autoantigens (including to calcium sensing receptor)
Autosomal dominant hypocalcaemia type 1	*CASR* mutation (3q21.1) (AD)
Autosomal dominant hypocalcaemia type 2	*GNA11* mutation (19p13.3)
22q11.2 deletion syndrome	Most common microdeletion syndrome in humans
DiGeorge syndrome (hypoparathyroidism)	1.5 to 3.0 hemizygous deletion of 22q11.2 (haploinsufficiency of *TBX1* gene). Sporadic
Velocardiofacial syndrome (hypoparathyroidism)	1.5 to 3.0 hemizygous deletion of 22q11.2 (haploinsufficiency of *TBX1* gene). (AD)
Kearns-Sayre syndrome (hypoparathyroidism)	Mitochondrial DNA abnormalities
Kenny-Caffey syndrome (hypoparathyroidism)	Mutations in gene encoding tubulin-specific chaperone E (*TBCE*) on 1q42-q43 (AD or AR)
Sporadic idiopathic hypoparathyroidism	Unknown. Antibodies to CASR. Sporadic
Autoimmune polyglandular syndrome type 1 (hypoparathyroidism)	*APECED* (autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy) or *AIRE* (autoimmune regulator) gene (21q22.3) mutation. (AR). Autoantigens to calcium sensing receptor
Familial isolated hypoparathyroidism	Various genes associated: *CASR* (3q13.3-21), *PTH* (11p15.3-p15.1), *GCM2* (6p24.2), *GCMB* (6p23-24), and X-linked form (Xq26-q27). Usually AD
Autosomal recessive hypoparathyroidism	*PTH* (11p15.3-p15.1) point mutation (AR)
Jansen's chondrodystrophy (hypoparathyroidism)	*PTHr1* (3p22-p21.1) mutation (AD)
Blomstrand's chondrodystrophy (hypoparathyroidism)	*PTHr1* (3p22-p21.1) mutation (AR)
Human hypoparathyroidism, sensorineural deafness and renal dysplasia (HDR)	Haploinsufficiency of *GATA3* gene (10p15) (AD)
Pseudohypoparathyroidism type 1a (Albright hereditary osteodystrophy)	*GNAS1* mutation (AD)
Pseudohypoparathyroidism type 1b	*GNAS1* mutation
Pseudohypoparathyroidism type 2	Defective cAMP-dependent protein kinase

AD: autosomal dominant.
AR: autosomal recessive.

Table 1

Somatic *MEN1* mutations can be identified in various solitary endocrine tumours. For example, somatic *MEN1* mutations are identified in 15–20% of sporadic parathyroid adenomas, and allelic loss on 11q are more common.[8,9] Although parathyroid carcinomas may show loss of heterozygosity of MEN1 as well as LOH of the *HRPT2* locus, and somatic *MEN1* mutations have been reported in sporadic parathyroid carcinomas.[10,11] Fluorescence in situ hybridization studies show frequent loss of chromosome 11 in parathyroid adenomas, and frequent gain of chromosome 11 in parathyroid carcinoma.[12] Cyclin D1/PRAD1 (parathyroid adenoma) gene (11q13) encodes cyclin D1, a regulator of cell cycle progression which has been found to be overexpressed in neoplastic parathyroid glands.[13] Approximately 5% of parathyroid adenomas have alterations of cyclin *D1/PRAD1*.

Multiple endocrine neoplasia type 2A (MEN2A)

MEN2A is associated with medullary thyroid carcinoma (90%), pheochromocytoma (50%), and parathyroid disease (20–30%).[14] The parathyroid glands are often asymmetrically enlarged and show increased numbers of chief cells which may have a nodular or a diffuse pattern. MEN2A occurs in an autosomal dominant pattern with almost complete penetrance. Approximately 95% of MEN2A patients have mutation in *RET* proto-oncogene (10q21) mutation in exon 10 or 11, with codon 634 most commonly affected.[15,16] There is some genotype–phenotype correlation with the codon involved used as a basis for surgical decisions. Mutations in codon 634 are associated with high penetrance and hyperparathyroidism and pheochromocytomas.[16,17] *RET* gene mutational analysis is used to confirm a diagnosis of MEN2, to screen family members, and in prenatal testing in families known to have *RET* mutation. Somatic RET