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Molecular analysis of the HPJ-JT syndrome and sporadic parathyroid carcinogenesis

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Chapter 1

Introduction and outline

Introduction

History

The parathyroid glands, the last major organ to be discovered in humans, were first recognized by Virchow (1863); however, it was Ivar Sandström (1852-1889) who is generally acknowledged as the first to describe these glands in detail.[44] Sandström demonstrated that the glands were structures separate from the thyroid and gave these organs their name of glandula parathyreoidea. He reported the number and histology of these glands, but the function of these glands remained unknown until 1891, when von Recklingshausen[50] reported the association between bone disease and hyperparathyroidsim (HPT).

Parathyroid glands

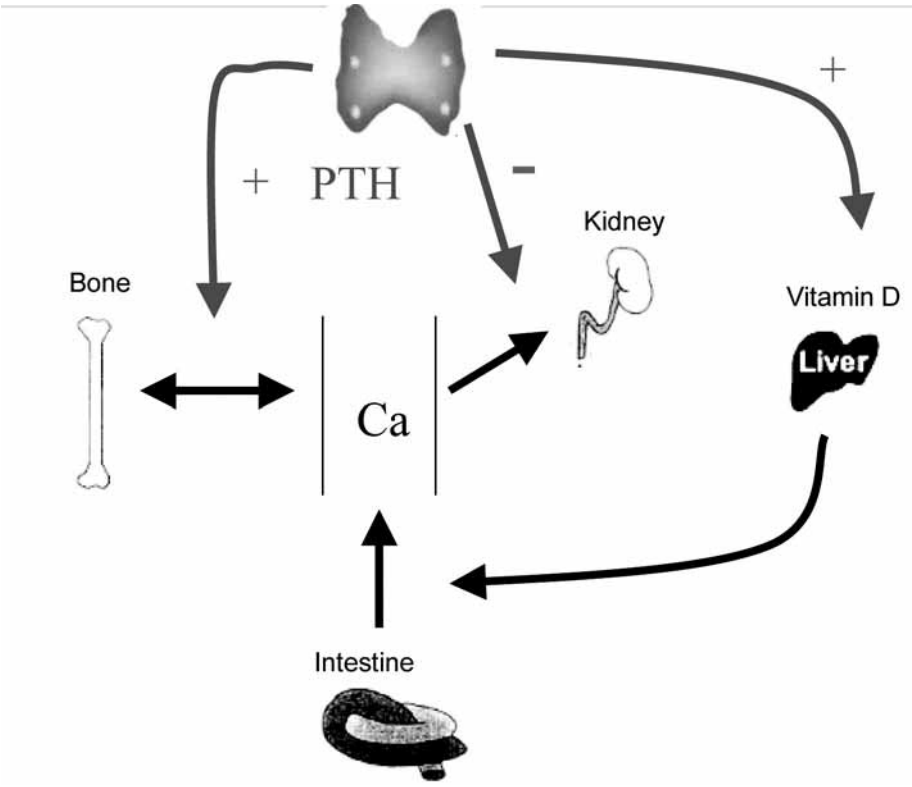
Normal gross anatomy and embryology
In the majority of cases, the parathyroid consists of four oval bone-shaped glands[25], two superior and two inferior. Five percent of people have supernumerary glands (defined as weight >5 mg and located apart from the other 4 glands).[16] The superior parathyroid gland arises from the fourth branchial (pharyngeal) pouch and descends into the neck with the thyroid gland. The inferior parathyroid glands, together with the thymus, are derived from the third branchial pouch.
The superior glands are most commonly localized in the fatty tissue on the middle third of the posterior lateral border of the thyroid gland, while the inferior glands are located on the lower thyroid poles close to the inferior thyroid artery.[5]
The mean weight of all four glands is approximately 120 mg in men and 130 mg in women.[16;25] Each gland has an average size of 4x3x1.5 mm, with the lower glands generally larger than the upper glands.[1] The colour varies from reddish brown to a yellow tan depending on the amount of stromal fat.
The arterial supply of the glands is derived from branches of the superior thyroid artery (upper parathyroid) and the inferior thyroid artery (lower parathyroid).
Venous drainage is achieved by the superior thyroid vene (upper parathyroid) and the inferior thyroid vene (lower parathyroid).[16]

Normal histology
The parathyroid glands are microscopically composed of three types of parenchymal cells interspersed with a varying amount of stroma surrounded by a thin connective tissue capsule. The parenchyma is composed of chief cells, oncocytic or oxyphilic cells and water clear cells.
Chief cells are small and regular cells with an amphophylic and relatively lucent cytoplasm. The nuclei are centrally located, with uniform chromatin and small inconspicuous nucleoli. They are often moulded and show overlap. These cells synthesize, transport, store, and secrete parathyroid hormone (PTH).[27;41]
Oncocytic or oxyphilic cells have a more abundant cytoplasm, which is deeply granular and acidophilic. These types of cells appear at puberty and increase in number as age progresses. The cells are often present in the form of clusters or nodular collections.
Water clear cells have an abundant and optically clear cytoplasm and sharply defined cell membranes. It is suggested that the water clear cells are inactive chief cells.[16]
The stromal component is composed of mature fat cells, blood vessels and a varying amount of connective tissue. Stromal fat cells begin to appear late in the first decade of life and increase throughout life, reaching a maximum in the third to fifth decades

of life.[16]
Parathyroid cells have a lifespan of approximately 20 yrs eventually undergoing apoptosis[52]. Mitoses are almost never seen in normal parathyroid cells.[40]

Physiology
Calcium plays a central role in a number of physiological processes that are essential for life including neuromuscular transmission, muscle contraction, cardiac automaticity, nerve function, cell division and movement and certain oxidative processes. Normal calcium concentrations are maintained as a result of tightly regulated ion transport by the kidneys, intestinal tract, and bone (see Figure 1). This is mediated by calcaemic hormones, in particular the parathyroid hormone (PTH) and the active form of Vitamin D.[24]

Figure 1



PTH is a linear polypeptide containing 84 amino acid residues, whose major function is to increase extracellular Ca^{2+} concentration. It is synthesized in the chief cells in parathyroid gland, in the form of a large precursor molecule: preproPTH, which is processed and shortened in the parathyroid cell. Once secreted, PTH has a half-life of approximately 2 minutes.
The primary function of PTH is to increase serum Ca^{2+} concentration and in this way maintain the extracellular fluid (ECF) calcium concentration within a narrow normal range. Secretion of PTH is regulated by extracellular calcium, via a G protein-coupled calcium-sensing receptor.[9]

The hormone stimulates calcium release from bone, reabsorption from the kidneys and uptake from the intestines.[12] The latter process is mediated by 1,25-dihydrocholecalciferol, which is the biological active form of Vitamin D3 (cholecalciferol). PTH is required to metabolise Vitamin D3, which is formed in the skin through the action of UV light, to 1,25-dihydrocholecalciferol in the liver.
A defect in the calcium sensing signalling cascade mentioned above can lead to hyperparathyroidism, characterized by inappropriately high levels of PTH in relation to extra cellular calcium levels and hyperplasia or increased cell proliferation.[10;11]

Hyperparathyroidism

Etiology
Increased cell proliferation manifests as hyperplastic or neoplastic parathyroid lesions. HPT may develop as a primary disorder, either idiopathic or familial, or as a secondary disorder in response to a biochemical imbalance, generally due to renal impairment. It may also arise in response to lithium treatment as a therapy for bipolar disorder. Secondary HPT may in turn progress to a tertiary disorder; the parathyroid hyperactivity becomes autonomous and is no longer responsive to physiological regulation. The mechanism and molecular pathway(s) underlying this phenomenon are unclear.

Parathyroid gland lesions
Primary hyperparathyroidism (PHPT) is caused by adenomas in 80% of the cases, hyperplasia in 20% and carcinoma in 1% of the cases
Hyperplasia is defined as an absolute increase in parathyroid parenchymal cell mass resulting from proliferation of chief cells, oncocytic cells and transitional oncocytic cells in multiple parathyroid glands in the absence of a known stimulus for PTH hypersecretion[15]
A parathyroid adenoma is a benign encapsulated neoplasm usually involving a single gland with an adjacent rim of normal glandular tissue. The presence of a microscopically normal second gland is thought to represent the best evidence that a given parathyroid lesion is an adenoma rather than hyperplasia.[15]
Carcinomas are malignant neoplasms derived from parathyroid parenchymal cells.[26]

Histology
Parathyroid tumours are genetically, clinically and histologically very heterogeneous lesions, which often makes the diagnosis difficult if not impossible.
Benign tumours (adenoma and hyperplasia) are treated with simple parathyroidectomy; however, there is an important distinction between adenoma and hyperplasia in that hyperplasia will recur or persist if only one gland has been removed. Intraoperatively, parathyroid carcinoma usually appears as a large, firm, whitish-gray tumour that commonly has invaded surrounding structures. Despite these defining characteristics, parathyroid carcinoma is often not recognized at the time of initial surgery.[43] In patients who undergo routine parathyroidectomy, as cancer is not suspected, 50% or more will develop local recurrence.[51] Furthermore, almost 90% of all patients with recurrent hyperparathyroidism will eventually die of the disease.[31] In contrast, patients where an adequate diagnosis was possible intraoperatively and treated by en bloc resection, local recurrence ranges from 10-33%, and long-term survival improves significantly.[31;53]
In summary, a quick (intra-operative) diagnosis of the three parathyroid tumours is essential as it has implications for (surgical) therapy.
However, intraoperative diagnosis is difficult, as there are almost no reliable differences between the tumours histologically. All three tumour types are characterized by the absence of intraparenchymatous fat and are composed of chief

cells, oncocytic cells or mixtures of these cell types. The only difference between adenoma and hyperplasia is the amount of affected glands and thus it is virtually impossible to differentiate between these two benign tumours purely on histological grounds.[19]
The distinction between parathyroid carcinoma and adenomas based on histology and morphology alone is also difficult. Some authors have claimed that trabecular growth, dense fibrous bands, spindle shape of tumour cells, mitotic figures and nuclear atypia[45] are helpful criteria to diagnose parathyroid carcinomas, but all these criteria can also be observed in benign parathyroid lesions.[7;34;46] Therefore, none of these characteristics are specific, although the presence of several in the same tumour increases the possibility of malignancy.[23] An unequivocal diagnosis of parathyroid carcinoma is only possible by demonstration of distant or local regional metastasis, characterized histologically by blood vessel invasion and/or capsular invasion.[42]
In conclusion, diagnostic accuracy of parathyroid tumours up until now has relied on multiple markers including the recognition of the constellation of macroscopic and microscopic features in combination with multidisciplinary correlation and not by histology alone. Based on recent insights, including work described in this thesis, histology might be supplemented by molecular investigations.

Primary hyperparathyroidism
PHPT is one of the most common endocrinopathies, with a prevalence of approximately 1-3 per 1000 individuals.[2] Sporadic PHPT is most common in post-menopausal women, with an estimated prevalence of 34 per 1000 individuals from this population subgroup.[33] The majority of tumours in primary hyperparathyroidism are sporadic. However, approximately 5% are associated with the autosomal dominant hereditary cancer syndromes Multiple Endocrine Neoplasia type 1 (MEN 1; OMIM #131100) and type 2A (MEN 2A; OMIM #171400), Hyperparathyroidism-Jaw Tumour Syndrome (HPT-JT, OMIM #145001), and Familial Isolated Hyperparathyroidism (FIHP, OMIM #145000).[35]
MEN1 syndrome is characterized by the occurrence of tumours of the parathyroids, pancreatic islet cells and anterior pituitary. PHPT represents the most common endocrinopathy in MEN1, reaching nearly 100% penetrance by age 40.[8] Parathyroid tumours occur in 95% of the MEN1 patients.[49]
The *MEN1* gene consists of 10 exons that encode a 610 amino acid protein, referred to as MENIN. MENIN appears to have a large number of potential functions through interactions with proteins that alter cell proliferation mechanisms.[49] The *MEN1* gene represents a tumour suppressor gene (TSG) and is located on chromosome 11q13. The majority of tumours (95%) show additional LOH consistent with Knudsen's two hit theory. MEN2 (OMIM 171400) is a rare autosomal dominant disorder of multiple endocrine neoplasms, including medullary thyroid carcinoma, pheochromocytoma, and parathyroid adenomas. Medullary thyroid carcinoma is the most prominent feature, as parathyroid tumours are found in 10-20% of affected family members.[30] MEN2 is caused by germline activating mutations of the *RET* proto-oncogene at 10q11.2[17;38].
HPT-JT (OMIM 145001) is an autosomal dominant syndrome characterised by parathyroid adenoma or carcinoma, ossifying fibroma of the mandible or maxilla, and renal lesions including Wilms tumour, renal cysts and tumours and uterine tumours.[14;22] About 80% of the patients present with hyperparathyroidism in late childhood or early adulthood[35]. The incidence of carcinoma in HPT-JT syndrome is reported to be 10-15%.[13;35] The high incidence of cystic change is another unique feature of parathyroid neoplasia in this syndrome.[34]
The gene causing HPT-JT is localized at chromosome 1q24-q32 and is known as the *HRPT2* gene (also known as Cdc73) and is thought to function as a tumour suppressor gene.[47]

A number of families with HPT alone (known as FIHP) have been described. A disease with an autosomal dominant pattern of inheritance, FIHP is known to be a genetically heterogeneous condition with germline mutations in *CASR* but also linkage to *MEN1*[48] and the *HRPT2* region.[37]

Sporadic parathyroid tumours

The etiology of sporadic HPT has long been unknown, until recently when several genetic mechanisms have been revealed that play a role in the development of sporadic parathyroid tumours. *CCND1* and *MEN1* have been established as having important roles in parathyroid tumourigenesis.
A translocation between *CCND1* and *PTH* resulting in the overexpression of *CCND1* has been found in a number of parathyroid adenomas. [6] Furthermore mutations in *MEN1* are reported in up to 30% of sporadic parathyroid adenomas.[18;28;36]

Chromosomal aberrations and genetic abnormalities in parathyroid tumours

Chromosomal losses and gains have been characterized in parathyroid tumours using comparative genomic hybridization and LOH studies. In general, parathyroid carcinomas show more chromosomal aberrations compared to adenomas (1.3x more losses and 3x more gains). In adenomas, more losses (2.7x) than gains have been found.
Regions frequently (in >10% of cases) lost in carcinomas are 1p, 13q, 6q, 9p, 4q, 18q and 2q. Regions frequently (in >10% of cases) gained in carcinomas are chromosomal regions xq, 1q, 16p, 9q, xp, 19q, 20q, 17q and 5q. Adenomas show frequently loss of chromosomal regions 11q, 11p, 15q, 1p, 13q and 22q. Gains are only seen in adenomas in chromosomal region 19p.[4;20;32;39]
Reports considering chromosomal changes in hyperplasia show conflicting results. Several studies using CGH[21] and LOH[29] report a relative lack of numerical chromosomal alterations (besides a gain of 12q in 11% of cases as reported by Imanishi et al). Other reported changes occurred in less than 10% of the cases, although Afonso et al[3] found by CGH analysis several regions with numerical changes.
Regions frequently lost in secondary hyperparathyroidism according this last study are 1p, 19p/q, 22p/q, 20q, 16q and 17p/q. Tertiary hyperplasia show in the same study losses in 1p, 20q, 12q, 19p/q and 22pq[3].
Gains are described in chromosomal region 6q, 13q, 5q, 4q and 12q in secondary hyperparathyroidism, tertiary HPT show gains in 4q and 6q. See Figure 2 for an overview.

FIGURE 2A

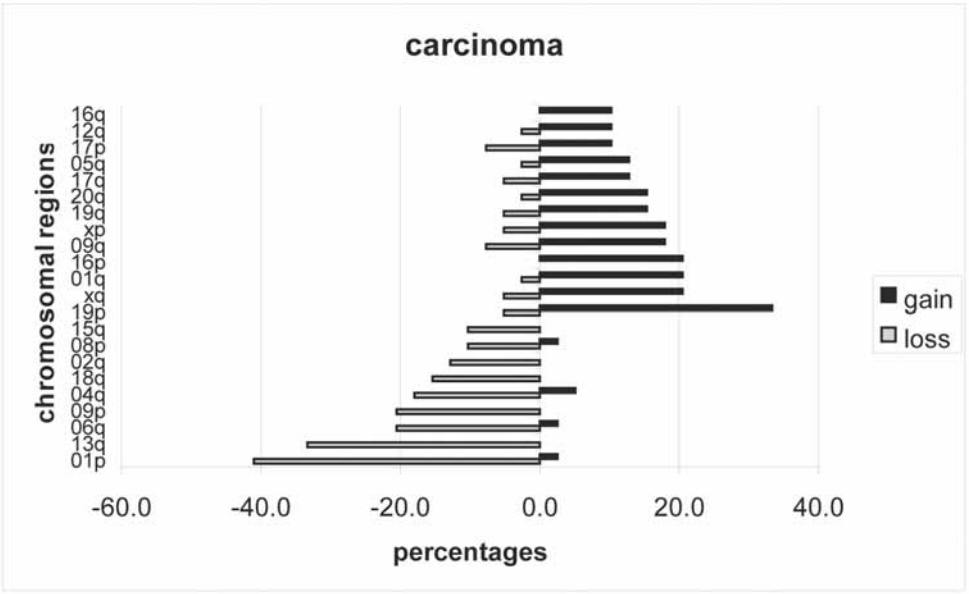


FIGURE 2B

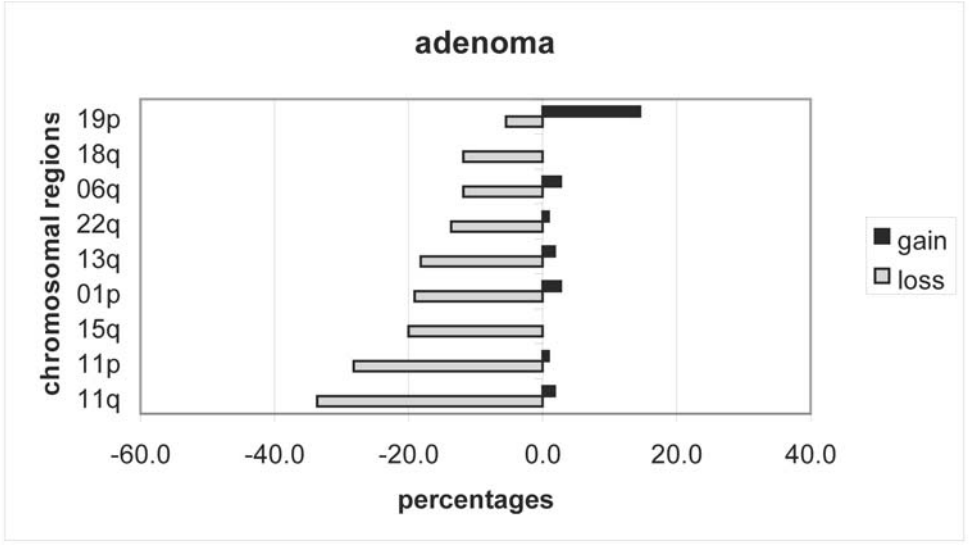


FIGURE 2C

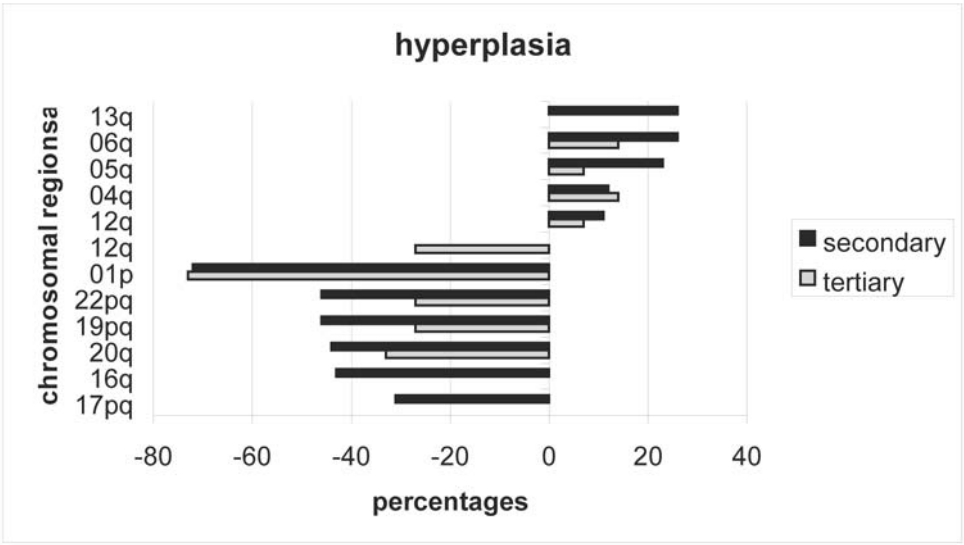


Figure 2 A, B and C depict the regions frequently (in >10% of cases) lost and gained in carcinomas (A) ,adenomas (B) and hyperplasia (C) found by CGH analysis.[3;4;20;32;39]. In C percentages of gains and losses are indicated in a similar way as in A/B.

Scope of this thesis

HPT-JT syndrome is a rare disease characterized by parathyroid tumours (with a high percentage of carcinomas), jaw and kidney tumours.
In this thesis, the clinical and genetic features of the HPT-JT syndrome and the relationship between the *HRPT2* gene and parathyroid tumours were investigated. Furthermore, we tried to gain insight in the molecular mechanisms of parathyroid tumourigenesis to improve the accuracy of diagnosis of these tumours.
Chapter 2 describes a clinical and histopathological study of a large kindred in which affected members presented with either parathyroid adenoma or carcinoma, although additional tumours were also found. Linkage analysis was performed to determine the genetics of this disease and the *HRPT2* region (locus associated with HPT-JT) was narrowed.
In ***chapter 3***, we refined the *HRPT2* region to 1q25-q32 by genotyping 26 affected kindreds. Furthermore, we report the identification of the gene responsible for the hyperparathyroidism–jaw tumour (HPT–JT) syndrome. The proposed role of *HRPT2* as a tumour suppressor was investigated by mutation screening in parathyroid adenomas with cystic features.
The *HRPT2* mutation status was determined in several types of parathyroid tumours in ***chapter 4*** including adenomas, carcinomas and hyperplasia both in a sporadic and familial context. Loss of heterozygosity analysis at 1q24-q32 was also performed on a subset of these tumours.
In ***chapter 5***, we hypothesize that loss of parafibromin, the protein product of the *HRPT2* gene, would distinguish carcinoma from benign tissue. We describe the immunohistochemical analysis of a newly generated antiparafibromin monoclonal antibody in mostly unequivocal carcinoma specimens, benign tumours en HPT-JT related tumours
In ***chapter 6***, morphological characteristics of primary parathyroid carcinomas and metastases were studied. Furthermore, immunohistochemical expression profiles were determined for parathyroid carcinomas, adenomas and hyperplasia using a tissue micro array. Loss of heterozygosity (LOH) of the chromosome 1q region containing the *HRPT2* gene and
chromosome 11q (*MEN1*) was determined in the carcinomas.
The aim of the study described in ***chapter 7*** was to further evaluate the role of *MEN1* and *HRPT2* mutations in sporadic formalin fixed paraffin embedded parathyroid tumours fulfilling histological criteria for malignancy. *HRPT2* and *MEN1* were analyzed by direct DNA sequencing in formalin fixed paraffin embedded parathyroid carcinoma tissue.
Chapter 8 describes a study based on microarray expression profiling of hereditary and sporadic benign and malignant parathyroid neoplasms to better define the molecular genetics of parathyroid tumours. A class discovery approach was used to identify distinct groups and gene sets able to distinguish between the groups. Several antibodies, selected based on the RNA profile, were analysed to discover potential useful markers for parathyroid carcinomas.
The aim of the study described in ***chapter 9*** was to find a method to rapidly screen parathyroid tumours for chromosomal aberrations. We applied a newly developed multiplex ligation-dependent probe amplification assay (MLPA) especially designed to detect genomic deletions and duplications in parathyroid neoplasms. Adenomas, carcinomas and normal tissue were analyzed.
Finally, ***chapter 10 and 11*** cover the concluding remarks, English summary and summary in Dutch, respectively.

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