Diagnosis and Management of Hereditary Thyroid Cancer

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Abstract

Thyroid cancers are largely divided into medullary (MTC) and non-medullary (NMTC) cancers, depending on the cell type of origin. Familial non-medullary thyroid cancer (FNMTC) comprises about 5–15 % of NMTC and is a heterogeneous group of diseases, including both non-syndromic and syndromic forms. Non-syndromic FNMTC tends to manifest papillary thyroid carcinoma, usually multifocal and bilateral. Several high-penetrance genes for FNMTC have been identified, but they are often confined to a few or single families, and other susceptibility loci appear to play a small part, conferring only small increments in risk. Familial susceptibility is likely to be due to a combination of genetic and environmental influences. The current focus of research in FNMTC is to characterise the susceptibility genes and their role in carcinogenesis. FNMTC can also occur as a part of multitumour genetic syndromes such as familial adenomatous polyposis, Cowden's disease, Werner's syndrome and Carney complex. These tend to present at an early age and are multicentric and bilateral with distinct pathology. The clinical evaluation of these patients is similar to that for most patients with a thyroid nodule. Medullary thyroid cancer (MTC) arises from the parafollicular cells of the thyroid which release calcitonin. The familial form of MTC accounts for 20–25 % of cases and presents as a part of the multiple endocrine neoplasia type 2 (MEN 2) syndromes or as a pure familial MTC (FMTC). They are caused by germline point mutations in the RET

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G. Pichert and C. Jacobs (eds.), *Rare Hereditary Cancers*,
Recent Results in Cancer Research 205, DOI 10.1007/978-3-319-29998-3_3

oncogene on chromosome 10q11.2. There is a clear genotype–phenotype correlation, and the aggressiveness of FMTC depends on the specific genetic mutation, which should determine the timing of surgery.

Keywords

Medullary Thyroid Cancer · Papillary Thyroid Cancer (non-medullary thyroid cancer) · Oncogenes · Tumour suppressor genes · Multiple Endocrine neoplasia · Genetic syndromes · Familial

Contents

1 Introduction

Thyroid cancer is the most prevalent endocrine malignancy. The incidence of primary epithelial cancer of the thyroid is 0.7 per 100,000 in males and 1.9 per 100,000 in females in the UK (Hodgson et al. 2014). The incidence of thyroid cancer today is 2.4 times what it was 3 decades ago. The rising incidence of thyroid cancer could be due to improved diagnostic procedures and advanced screening, but the increase in the diagnosis of significantly larger tumours cannot be attributed to improved screening alone (Davies and Welch 2006; Chen et al. 2009). Radiation is the most important environmental predisposing factor for epithelial thyroid cancer.

The cell line from which the cancer originates determines the subtype: parafollicular C cells for medullary thyroid cancer (MTC) and follicular cells for non-medullary thyroid cancer (NMTC). Differentiated thyroid carcinoma (DTC) comprises approximately 90 % of all cases of NMTC and consists of 2 distinct histological types: papillary thyroid cancer (PTC, 80–90 % of cases) and follicular (FTC, 10 %). Less frequent types are Hürthle cell carcinomas, anaplastic (undifferentiated) carcinomas and squamous cell carcinomas.

Other non-epithelial malignancies that may be observed in the thyroid include lymphomas and sarcomas. Rarely, thyroid paragangliomas have been reported, and germline mutations in *SDHA* and *SDHB* have been detected in confirmed thyroid paraganglioma cases (von Dobschuetz et al. 2015).

The aetiology of DTC is largely unknown and may vary according to histological type. The majority of PTC and FTC are sporadic, and familial tumours may account for 5–15 % of thyroid carcinoma cases. These can be syndromic or non-syndromic. A number of epidemiological studies have examined the risk of DTC in relation to family history of thyroid disease and cancer. Many reported familial clusters of thyroid cancer and several studies of families with clustering of thyroid cancer demonstrate a more aggressive clinical course (Pal et al. 2001; Frich et al. 2001; Hemminki and Dong 2000). Increased risk of DTC associated with a family history of thyroid cancer has been observed in most case–control and Cancer Registry studies, and thyroid cancer has one of the highest familial risks of all cancers. The reported excess risk in relatives of index cases ranges from twofold to tenfold. Individuals with a family history of PTC in first-degree relatives also have an increased risk of PTC, this excess risk being greater in subjects who report a family history of thyroid cancer in siblings (Xu et al. 2012). Additionally, among patients with PTC, those with a family history of thyroid cancer tend to develop multifocal primary tumours more frequently than those without a family history of thyroid cancer (Uchino et al. 2002).

2 Familial Non-medullary Thyroid Cancer (FNMTC)

FNMTC is defined as the presence of well-differentiated thyroid cancer (WDTC) of follicular cell origin in two or more first-degree relatives. FNMTC encompasses a heterogeneous group of diseases, including both non-syndromic and syndromic tumours (Sturgeon and Clark 2005).

The non-syndromic group of patients with FNMTC have familial follicular-derived NMTC in the absence of a specific genetic syndrome. However, most patients with FNMTC have familial papillary thyroid cancer (FPTC). Thyroid cancers in FNMTC have a well-documented predisposition to be multicentric, bilateral disease with early local invasion, extrathyroidal extension and lymph node metastases. These cancers have an increased risk of recurrence and have characteristic histology. The background thyroid may show lymphocytic thyroiditis, multinodular hyperplasia and multiple adenomatous nodules. Benign thyroid disease such as multinodular goitre, thyroiditis and other neoplasms occurs with increased frequency in this group of patients (Musholt et al. 2000). A large population-based study from five Nordic countries found the cumulative risk of WDTC by age 60 in relatives of FNMTC cases to be 46 times that of the general population (9.2 vs. 0.2 %), and 164 times in at-risk men (14.8 vs. 0.09 %). It is important to remember that even individuals with apparently sporadic WDTC may be part of unrecognised FNMTC kindred due to incomplete penetrance, incomplete family history or as yet unidentified disease in other family members.

Numerous somatic genetic abnormalities are detected in sporadic papillary thyroid cancers. *RET/PTC* rearrangements were the first genetic abnormalities to be associated with sporadic papillary thyroid cancers. *RET* rearrangements occur most often in papillary thyroid cancers associated with radiation exposure and in children. *RET/PTC1* and *PTC3* rearrangements are the most frequent alterations, and 15 *RET* rearrangements have been documented (Navas-Carrillo et al. 2014; Grogan et al. 2010). *RET/PTC* mutations have been reported both to be associated with more and with less aggressive thyroid cancers, so probably do not influence tumour behaviour (Giordano et al. 2005). A somatic *BRAF* point mutation is the most common abnormality in sporadic PTC and is found in about 50 % of these tumours. Most but not all reports suggest that *BRAF* mutations are more commonly associated with aggressive pathological parameters, radioiodine refractory, lymph node metastasis and increased cancer mortality. However, some reports suggest that up to 80 % of papillary thyroid cancers have a *BRAF* mutation, thus decreasing its prognostic value (Vasko et al. 2005; Xing et al. 2005). Somatic *RAS* mutations are reported to be more common in FTC than in PTC. *RAS* mutations are also found in some benign thyroid tumours. *TRK* mutations are found in about 5–15 % of PTCs (Grieco et al. 2009). *Pax 8/PPAR* gamma mutations are most often identified in follicular thyroid cancers but also occur in follicular adenomas (Krol et al. 2000). *p53* mutations are almost exclusively found in anaplastic thyroid cancers and in thyroid cancer cell lines. They may also be present in poorly differentiated thyroid cancers (Jossart et al. 1996).

3 Genetics of Non-syndromic FNMTC

The causative genes for FNMTC are largely unknown, though many candidates have been excluded, e.g. *RET*, *RAS*, *PTEN* and *BRAF* (Bonora et al. 2010). Several susceptibility loci have been identified by genetic linkage analysis in FNMTC families, including the *TCO* (thyroid cancer with oxyphilia) locus on chromosome 19p13.2 (Canzian et al. 1998), the *PRN1* locus on chromosome 1q21 (Malchoff et al. 2000) and the *NMTC1* locus on chromosome 2q21 (Mckay et al. 2001). There is also some evidence for the interaction of the *TCO* and *NMTC1* loci leading to increased risk in a small subset of FNMTC families. Other loci are being identified (see Table 1), but given that each has only been found in 1 or a few families, none accounts for the majority of FNMTC cases.

Germline mutations in *DICER* in man have been found to predispose to thyroid disease, notably multinodular goitre, and in mice, there is evidence of early neoplastic changes in the thyroid gland in mutation carriers, but there is no clear association with thyroid cancer in man (Slade et al. 2011). Germline alterations in the *ATM* gene may also be associated with increased papillary thyroid cancer risk (Gu et al. 2014). Some studies have revealed that common germline variants in the *RET* proto-oncogene, DNA repair genes *XRCC1*28 and *XRCC3*29 and xenobiotic metabolising genes *GSTT1* and *GSTM1* are significantly associated with DTC risk (Xu et al. 2012).

Table 1 Gene loci associated with thyroid cancer susceptibility

Tumour type	Gene	Chromosome	Inheritance
Familial multinodular goitre with progression to PTC	Unknown	14q31	[a]AD (Bignell et al. 1997)
PTC with papillary renal neoplasia	*PRN1* locus	1q21	Unknown (Malchoff et al. 2000)
Thyroid cancer with oxyphilia	Unknown/TCO/TIM44	19p13.2	[a]AD (Canzian et al. 1998)
Follicular variant of PTC (Ca type 1)	*NMTC1*	2q21	Unknown (Mckay et al. 2001)
Familial PTC	Unknown	8p23.1-p22	Unknown (Cavaco et al. 2008)
PTC	Unknown	1q21 and 6q22	Unknown (Suh et al. 2009)

[a]*AD* autosomal dominant

Some families have been reported with linkage to 14q, 19p, 2q, 1q, 8p, 6q and 12q, and many of these loci have been replicated by GWAS studies, but few candidate genes have yet been identified, and those that are being defined are usually regulatory (e.g. *SRGAP1* on 12q14), which regulates CDC42, which in turn acts as a signal convergence point in intracellular signalling networks). One family with multiple cases of NMTC showed linkage with a mutation in an enhancer region of 4q32 with binding sites for the POU2F1 and YY1 transcription factors.

Most highly penetrant mutations are only seen in isolated families, and the current evidence is for a few rare high-penetrance genes and a larger number of lower penetrance variants which contribute to thyroid cancer risk (Nagy and Ringel 2015; Nosé 2011).

4 Genetics of Syndromic FNMTC Cancers

Thyroid carcinomas may occur in several different multitumour genetic syndromes. These cancers are heterogeneous and tend to have an early age at diagnosis, and be multicentric and bilateral. The pathology of these tumours is distinct and should alert the clinician to the possibility of a familial cancer syndrome (Mazeh and Sippel 2013).

A number of syndromes are associated with an increased risk of NMTC. These include familial adenomatous polyposis (FAP), Cowden syndrome, Gardner's syndrome, Werner's syndrome and Carney complex.

Familial adenomatous polyposis (FAP) is an autosomal dominant disease characterised by gastrointestinal polyposis and colorectal cancers. It is caused by a germline mutation in the *APC* gene. Thyroid cancer is a rare manifestation (cumulative risk 2.8 % by age 60) and is usually multifocal and bilateral with a

characteristic cribriform pattern which differentiates it from sporadic papillary cancer. Thyroid cancer mainly occurs with germline mutations between codons 1286 and 1513 of the *APC* gene. About 10 % of patients have metastases at the time of diagnosis. Mesodermal tumours (desmoids, osteomata of the skull) and congenital hypertrophy of the retinal pigment epithelium (CHRPE) may occur in addition to colonic polyposis (Xu et al. 2003). Gardner syndrome is characterised by colonic polyposis typical of FAP together with osteomas and soft tissue tumours. Screening by thyroid ultrasound examinations has been advocated.

Cowden syndrome is characterised by hamartomas, multiple papillomas, breast cancer, colonic polyps and thyroid disease. The underlying mutation is in *PTEN* although some cases are due to germline *KILLIN* methylation, and germline mutations in *SDHD* and *SDHB* may cause conditions mimicking some features of Cowden that is dominantly inherited (Bennett et al. 2010).

The thyroid cancer in Cowden syndrome, which is usually papillary, is often preceded by multinodular goitre, and early histology shows microscopic follicular adenomas. Thyroid disease both benign and malignant occurs in about two-thirds of subjects. Follicular thyroid cancer is more common in patients with germline *PTEN* mutations than those with *SDHX* and *KILLIN* alterations. *PTEN* frameshift mutations were found in 31 % of patients with thyroid cancer in Cowden syndrome compared to 17 % in those without thyroid cancer (Ngeow et al. 2011).

The autosomal recessive condition, Werner's syndrome, is caused by germline mutations in the *WRN* gene. Premature ageing begins in adolescence and early adulthood, and features include scleroderma-like skin changes, cataracts and a high incidence of neoplasia. Thyroid cancer, predominantly follicular, may occur (Ishikawa et al. 1999).

Carney complex is an autosomal dominant condition characterised by myxomas, pigmentation of the skin and mucosa and endocrine overactivity. The condition is caused by mutations in the *PRKAR1α* gene. Approximately 11 % of patients have thyroid pathology including adenomatous hyperplasia, follicular or papillary hyperplasia and PTC (Stratakis et al. 1997).

There are less well-established associations of non-medullary thyroid carcinoma with multiple endocrine neoplasia type 1 (MEN 1), McCune-Albright syndrome, Peutz–Jegher's syndrome and Ataxia–telangectasia (Harach 2001; Yang et al. 1999). Multiple endocrine neoplasia type 4 (MEN 4), a rare condition in individuals with germline mutations in p27Kip1 (*CDKN1B*), who present with endocrine lesions in the MEN 1 spectrum (commonly parathyroid and pituitary adenomas), is occasionally associated with papillary thyroid cancer (Molatore et al. 2010) (Table 2).

Table 2 Syndromes associated with an increased risk of thyroid cancer

Syndrome	Gene	Chromosome	Inheritance	Incidence of thyroid cancer	Type of thyroid cancer
Familial adenomatosis polyposis (FAP)	*APC*	5q21	AD	2–12 %	PTC cribriform-morular or classical variant
Gardner's syndrome	*APC*	5q21	AD	10 %	PTC cribriform or classical variant with sclerosis
Peutz–Jeghers' syndrome	*STK11/ LKB1*	19p13.3.	AD	Rare	PTC
Cowden's disease	*PTEN*	10q22-23	AD	>10 %	Follicular and occasional PTC
PTEN hamartoma tumour syndrome (PHTS)	*PTEN*	10q22-23.3	AD	5–10 %	Follicular, occasional PTC and anaplastic
Werner's syndrome (in Japanese)	*WRN*	8p11-21	AR	18 %	Follicular, anaplastic and PTC
Carney complex	*PKAR1A*	17q24	AD	4 and 60 %	Follicular and PTC
McCune-Albright syndrome	*GNAS1*	20q13.1-13.2	[a]Mosaic		Clear cell thyroid carcinoma

[a]Mosaic denotes the presence of two or more populations of cells with different genotypes in one individual who has developed from a single fertilised egg

5 Management of FNMTC

Despite common features, familial thyroid cancers are heterogeneous, show diverse natural histories and require better characterisation in distinguishing one type from another. The identification of hereditary cases and early diagnosis makes preventive surgery and adequate treatment possible, with improved outcomes for patients and their families.

The initial management of FNMTC includes a detailed family history and the exclusion of known syndromes. A history of radiation exposure is also important. The clinical evaluation of patients with FNMTC is similar to that for most patients with a thyroid nodule. Although there are no established guidelines for screening relatives of index cases with FNMTC, in those with a normal thyroid gland documented by physical examination, an ultrasound examination is recommended beginning at age 10. This could continue on an annual basis. When a suspicious nodule or nodules are identified, fine needle aspiration (FNA) for cytological examination is recommended. FNA may not be as accurate in these patients because of the multifocal nature of these tumours and coexisting benign thyroid nodules that are also more common than in patients with sporadic thyroid tumours. Metastatic disease may be the first presentation in these patients.

Given the aggressive nature of the disease and the low sensitivity of FNA cytology in FNMTC, the treatment of choice in a patient with a strong family history and a nodule is total thyroidectomy. Ipsilateral or bilateral central neck dissection and post-operative radioactive iodine ablative therapy along with thyroid stimulating hormone (TSH) suppression should be considered depending on the preoperative staging. The administration of radioiodine 1-131 is aimed at ablating any remnant thyroid tissue and potential microscopic residual tumour. This procedure decreases the risk of regional recurrence and facilitates the long-term surveillance based on serum thyroglobulin (Tg) measurement and diagnostic radioiodine whole-body scan (WBS). Thyroid hormone suppression therapy is an important part of the treatment of thyroid cancer. TSH suppressive treatment with levothyroxine (LT4) is of benefit in high-risk thyroid cancer patients. Treatment of regional disease is based on the combination of surgery and radioiodine therapy. External beam radiotherapy may be indicated when complete surgical excision is not possible or when there is no significant radioiodine uptake in the tumour. Distant metastases are more successfully cured if they take up radioiodine and are of small in size. Chemotherapy is not effective. Approximately 12 % of FNMTC has persistent disease and 44 % develops recurrences emphasising the importance of follow-up. Metastatic disease is managed as for sporadic cases (Mazeh and Sippel 2013; Rivkees et al. 2011).

6 Medullary Thyroid Carcinoma (MTC)

MTC is a well-differentiated rare thyroid tumour that arises from the parafollicular- or calcitonin (CT)-producing C cells derived from the neural crest. Its origin makes it a separate entity from the other DTC. It releases several neuroendocrine peptides, and these include calcitonin and carcinoembryonic antigen (CEA), which are useful tumour markers. It occurs in sporadic and familial forms.

Both sporadic and familial (F) MTC arise at the junctions of the upper and middle thirds of the lateral lobes, corresponding to the areas where C cells are present. The overall prevalence comprises 5–10 % of all thyroid malignancies and about 15 % of all thyroid cancer-related deaths. It is present in less than 1 % of thyroid glands at autopsy. The clinical presentation of MTC occurs mainly in the fourth and fifth decades, but a wide range of ages at diagnosis has been observed.

The familial form of MTC accounts for 20–25 % of cases and presents as a part of the MEN 2 syndromes or as a pure familial MTC (FMTC). MEN 2 syndrome consists of three variants: multiple endocrine neoplasia type 2a (MEN 2A), multiple endocrine neoplasia type 2b (MEN 2B) and FMTC . Genotype–phenotype correlations in MEN 2 and/or FTMC are well established.

7 Sporadic MTC

This accounts for about 80 % cases of MTC. These are typically unilateral and have no associated endocrinopathies. Peak age at diagnosis is between 40 and 60 years, with a mean age 50 years and more common in females. One-third of the patients will present with intractable diarrhoea due to increased gastrointestinal secretion and hypermotility that is caused by raised calcitonin levels.

8 Familial or Inherited Medullary Carcinoma Without Associated Endocrinopathies

This form is the least aggressive. It usually presents as a thyroid nodule. This group of MTC patients usually have no other clinical manifestations. The peak incidence is between the ages of 40 and 50 years (Mears and Diaz-Cano 2003).

9 MEN 2A (Sipple Syndrome)

MEN 2A syndrome patients tend to have bilateral medullary carcinoma or C-cell hyperplasia (CCH), pheochromocytoma and hyperparathyroidism. This syndrome is inherited as an autosomal dominant manner. Peak incidence of medullary carcinoma in these patients is in the 30s but can present in late adolescence or early adulthood. Males and females are equally affected. An association with cutaneous lichen amyloidosis (CLA), a characteristic pigmented and itchy skin lesion specifically localised in the interscapular region of the back, has been reported in less than 10 % of MEN 2A families and is associated with a specific *RET* 634 mutation. When present, CLA is almost invariably diagnostic of MEN 2A and may be considered pathognomonic.

10 MEN 2B

MEN 2B syndrome is characterised by young age at onset MTC and pheochromocytoma, but only rarely hyperparathyroidism. These patients have an unusual appearance, which is characterised by mucosal ganglioneuromas and a marfanoid habitus. Inheritance is autosomal dominant. MEN 2B patients usually develop medullary carcinoma early in life, diagnosed in infancy or early childhood, and males and females are equally affected.

MTC typically is the first abnormality observed in both MEN 2A and MEN 2B syndromes.

Thyroid pathology in FMTC cases usually is characterised by multiple and bilateral tumours, associated with neoplastic CCH and a tendency to early lymph node metastases (Metzgera and Milasb 2014; Ganeshan et al. 2013) (Table 3).

Table 3 Clinical features of the different forms of MTC

Clinical presentation	Inheritance	Features of MTC	Associations
Sporadic MTC	None	Unifocal	None
MEN 2A	Autosomal dominant	Multifocal, bilateral	Pheochromocytoma (42 %) Hyperparathyroidism (10–30 %) Cutaneous lichen planus amyloidosis (rare) Hirschsprung disease (rare)
MEN 2B	Autosomal dominant	Multifocal, bilateral	Pheochromocytoma (40 %) Multiple mucosal neuromata (>95 %) Marfanoid body habitus (80 %)
FMTC	Autosomal dominant	Multifocal, bilateral	None

Hereditary MTC is caused by a germline point mutation in the *RET* oncogene on chromosome 10q11.2. The *RET* oncogene has 21 exons distributed over 60 kb. About 85 % of all mutations responsible for FMTC are well known. In the majority of MEN 2A and FMTC patients, mutations are clustered in six cysteine residues (codons 609, 611, 618 and 620 in exon 10, and codons 630 and 634 in exon 11) in the *RET* cysteine-rich extracellular domain. These mutations have been detected in about 95 % of MEN 2A and 85 % of FMTC families. Somatic *RET* point mutations have been identified in the tumour in about 50 % of patients with sporadic MTC.

The clinical course and prognosis of MTC depend on whether it is hereditary or sporadic and the type of *RET* mutation present. Sporadic MTC can present at any age, and it is usually associated with a palpable mass and the presence of nodal metastases.

11 Genotype and Phenotype

Since the initial discovery of *RET* mutations responsible for MEN 2, more than 50 different point mutations across 7 exons (exons 8, 10, 11, 13–16) have been identified. Different mutations in the *RET* gene produce varying phenotypes of the disease, including age of onset and aggressiveness of MTC, and the presence or absence of other endocrine tumours. This should determine the timing and extent of surgery (Krampitz and Norton 2014).

Approximately 98 % of patients with MEN 2 have mutations in the cysteine-rich extracellular domain, especially codons 609, 611, 618, 620 and 634 of exons 10 and 11, and 85 % have a mutation of codon 634 of exon 11. Early aggressive behaviour and metastasis in MEN 2A and MEN 2B are particularly associated with *C634* and *M918T* mutations. This requires early intervention. The *883RET* mutation displays a more indolent form of MTC compared with the *M918T* mutation for MEN 2B. A polymorphism at codon 836 is associated with early metastases in patients with hereditary or sporadic MTC. A mutation at codon 918 is almost exclusively found in MEN 2B.

12 Genetic Testing and Risk Stratification

Genetic testing detects germline *RET* mutations in most individuals with MTC, and predictive testing is offered to all first-degree relatives of patients with newly diagnosed hereditary MTC. Due to the varying clinical effects of *RET* mutations, strategies based on clinical phenotype, age of onset and aggressiveness of MTC are used to guide the management.

In 2010, the North American Neuroendocrine Tumor Society (NANETS) published consensus guidelines for the diagnosis and management of MTC. These guidelines were developed by classifying *RET* mutations into 3 groups based on aggressiveness of MTC or levels of risk. Table 4 summarises the 3 groups of MTC risk levels and the recommendations for the timing of prophylactic thyroidectomy based on these risk levels (Wu et al. 2011; Elisei et al. 2012).

MTC patients with advanced disease have metastases to regional lymph nodes or distant sites such as brain, bone, lung and liver. In these patients, thyroidectomy with nodal clearance is rarely curative. Some patients undergo repeat operations to remove residual tumour. Distant metastases limited to a single organ can be considered for curative surgical resection or another treatment modality, such as radiofrequency ablation or external beam radiation therapy. Chemotherapy is ineffective in patients with MTC, and the responses that occur are short-lived. External beam radiotherapy may improve regional disease control, but survival is not increased.

Recently, several molecular-targeted therapeutics (MTTs) have been used in clinical trials of patients with locally advanced or metastatic MTC. The most effective agents are the multityrosine kinase inhibitors, vandetanib and

Table 4 NANETS classification of MTC risk levels and management recommendations

NANETS risk level for MTC	Most common codon mutations	Age at prophylactic thyroidectomy
Level 1	609 630 768 790 791 804 891	By 5–10 years of age By 5–10 years because of variability in onset of tumours in some families
Level 2	611 618 620 634	By 5 year of age By 5 years of age
Level 3	883 918 922	Within the first 6 months of life (preferably in the first month of life)

cabozantinib, approved by the US Food and Drug Administration (FDA) for patients with advanced MTC. Other multikinase inhibitors include sorafenib, axitinib and motesanib. Measurements of serum markers calcitonin (CT) and CEA are important in the post-surgical follow-up of patients with MTC because they reflect the presence of persistent or recurrent disease. After surgery, serum CT levels normalise (undetectable) in 60–90 % cases of patients with no lymph node involvement but only in 20 % of those with lymph node metastases (Sakorafas et al. 2008; Daumerie et al. 2013).

13 Ongoing Research

The field of the genetics of endocrinology is advancing rapidly. The main thrust of current research in FNMTC is to characterise the susceptibility genes which are being identified by linkage analysis and genome-wide association studies. The single nucleotide polymorphism (SNP) on 9q22-23, for instance, lies within the linkage disequilibrium region where the *FOXE1*, *XPA*, *HEMGN* and *C9orf156 genes* lie, and the association with *FOXE1* has also been shown by an independent candidate gene association study. The *FOXE1* and *NKX2-1* genes have prominent roles in thyroid development and differentiation and have altered expression in thyroid tumours. They may alter the levels of TSH, and free T3 and T4. The role of genes that regulate the expression of these genes is being studied. These genes are central to a regulatory network of transcription factors, and alterations in the genes involved may be related to thyroid cancer susceptibility (Kula et al. 2010). The SNP on 14q13.3 is located in the linkage disequilibrium region containing *BRMS1L*, *MBIP*, *SFTA3* and *NKX2-1*, the latter of which is also involved in thyroid development, and has altered levels in thyroid tumours. Variants in this gene appear to be associated with altered levels of serum TSH, and further work is required to elucidate the role of these genes in PTC development. Other genes that may play a part in NMTC susceptibility are microRNA genes, such as miR-221 and miR-222, and further work is underway to elucidate their role. Further areas of study are the part played in the aetiology of well-defined syndromes, by newly identified genes that cause already well-defined syndromes such as Cowden syndrome, with *KILLIN* and *SDHD* and *SDHB* (von Dobschuetz et al. 2015).

Studies of the somatic genetic changes that occur in the development of NMTC will allow further differentiation of these cancers into subtypes with different molecular and environmental causes and lead to the development of improved targeted treatments.

In the field of MTC, much work is being done to define the genotype/phenotype correlations, which are very helpful in guiding clinical management of germline mutation carriers.

14 Summary

Thyroid cancers are largely divided into medullary and non-medullary cancers, each with many subtypes. About 20–25 % of MTC cases occur in the context of inherited syndromes due to different germline *RET* mutations, which are well-defined entities with clear genotype–phenotype correlations and agreed management protocols. NMTC is often familial but as yet the genetic factors involved in susceptibility to NMTC are ill-understood. Several high-penetrance genes for these tumours have been identified in families with several cases of NMTC, but other loci appear to play a small part, conferring only small increments in risk, such that the familial component in NMTC susceptibility is likely to be due to a combination of genetic factors and environmental influences which currently makes genetic testing quite difficult

Key points

- Assessment of the possibility of a hereditary thyroid cancer syndrome should be a part of first clinical episode in a patient with benign or malignant thyroid disease.
- A history of papillary thyroid carcinoma in two or more first-degree relatives should raise the question of FNMTC and more aggressive cancer.
- The initial management of FNMTC should include a detailed family history and the exclusion of known syndromes. A history of radiation exposure is also important.
- Ultrasound-based screening for thyroid disease should be a part of long-term surveillance in patients with multitumour genetic syndromes causing a predisposition to thyroid cancer.
- Lifetime cancer risks, including thyroid cancer, have been defined for individuals with *PTEN* and other susceptibility gene mutations.
- Risk stratification by *RET* gene mutation, and new medical therapies, are available for patients with hereditary MTC.
- North American Neuroendocrine Tumor Society (NANETS) consensus guidelines are useful in the diagnosis and management of MTC.
- Measurements of serum markers calcitonin (CT) and carcinoembryonic antigen (CEA) are important in the post-surgical follow-up of patients with MTC because they reflect the presence of persistent or recurrent disease.
- Serum CT level normalises (undetectable) in 60–90 % cases of patients with no lymph node involvement but only in 20 % of those with lymph node metastases after surgery.

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