

ORIGINAL ARTICLE

Early Malignant Progression of Hereditary Medullary Thyroid Cancer

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ABSTRACT

BACKGROUND

An age-related progression from C-cell hyperplasia to medullary thyroid carcinoma is associated with various germ-line mutations in the rearranged during transfection (RET) proto-oncogene that could be used to identify the optimal time for prophylactic surgery.

METHODS

In this European multicenter study conducted from July 1993 to February 2001, we enrolled patients who had a RET point mutation in the germ line, were 20 years of age or younger, were asymptomatic, and had undergone total thyroidectomy after confirmation of the RET mutation. Exclusion criteria were medullary thyroid carcinomas of more than 10 mm in greatest dimension and distant metastasis.

RESULTS

Altogether, 207 patients from 145 families were identified. There was a significant age-related progression from C-cell hyperplasia to medullary thyroid carcinoma and, ultimately, nodal metastasis in patients whose RET mutations were grouped according to the extracellular- and intracellular-domain codons affected and in those with the codon 634 genotype. No lymph-node metastases were noted in patients younger than 14 years of age. The age-related penetrance was unaffected by the type of amino acid substitution encoded by the various codon 634 mutations. The codon-specific differences in the age at presentation of cancer and the familial rates of concomitant adrenal and parathyroid involvement suggest that the risk of progression was based on the transforming potential of the individual RET mutation.

CONCLUSIONS

These data provide initial guidelines for the timing of prophylactic thyroidectomy in asymptomatic carriers of RET gene mutations.

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POINT MUTATIONS IN THE REARRANGED during transfection (RET) proto-oncogene¹ have emerged as the molecular basis of an array of distinct clinical phenotypes^{2,3} as diverse as Hirschsprung's disease (aganglionosis of the submucosal and myenteric plexus of the colon), familial medullary thyroid carcinoma, and multiple endocrine neoplasia (MEN) type 2A (MEN-2A, characterized by medullary thyroid carcinoma, pheochromocytoma, and parathyroid adenoma) and type 2B (MEN-2B, characterized by medullary thyroid carcinoma, pheochromocytoma, intestinal ganglioneuromatosis, and skeletal deformity).⁴ Encoding a receptor tyrosine kinase on chromosome 10q11.2, RET germ-line mutations in humans affect essentially four types of tissue, all of which originate from neural crest cells: thyroid C cells, parathyroid cells, chromaffin cells of the adrenal medulla, and enteric autonomic plexus.⁴

Paradoxically, point mutations involving the extracellular RET codons 609, 618, and 620 may exert a dual effect, causing both loss of function (Hirschsprung's disease) and gain of function (familial medullary thyroid carcinoma, MEN-2A, or MEN-2B). Loss of function results from a decrease in RET levels at the cell surface. Gain of function results from impaired disulfide bonding of two adjacent RET molecules owing to steric hindrance.⁵ The mechanisms of the gain-of-function mutations depend on the position of the RET germ-line mutation.⁴ Mutations involving extracellular-domain codons 609, 611, 618, 620, 630, and 634 activate the tyrosine kinase receptor by ligand-independent dimerization and cross-phosphorylation. Intracellular-domain mutations affect only codons 768, 790, 791, 804, and 891 and may interfere with intracellular ATP binding of the tyrosine kinase receptor. The M918T genotype causes alterations in the substrate-recognition pocket of the catalytic core.⁴

The various mechanisms of RET activation might determine the pace of malignant transformation from C-cell hyperplasia to medullary thyroid carcinoma, the first and most commonly fatal neoplasm among RET gene carriers, because of its overall high penetrance.⁶ By analogy, in transgenic-mouse models, animals harboring the MEN-2A (C634R) and MEN-2B (M918T) transgenes had overt C-cell hyperplasia at three weeks of age, and multifocal medullary thyroid carcinomas ultimately developed.⁷⁻¹⁰ These experimental data and preliminary studies of carriers of RET gene mutations^{11,12} support the concept of an age-related penetrance of hereditary

medullary thyroid carcinoma. Such genetic information might be used to help individualize the timing of prophylactic surgery. The multicenter European Multiple Endocrine Neoplasia (EUROMEN) study was devised to investigate the pace of early malignant progression to hereditary thyroid carcinoma among asymptomatic carriers of RET gene mutations.

METHODS

SELECTION OF PATIENTS

A standardized questionnaire was sent to all major European referral centers that specialize in surgery for MEN type 2 (MEN-2) and medullary thyroid carcinoma. Patients were eligible for inclusion in the EUROMEN multicenter study if they had evidence of a RET point mutation in the germ line, were 20 years of age or younger, were clinically asymptomatic, and had undergone total thyroidectomy after genetic confirmation of the RET point mutation. To avoid enrolling symptomatic index patients with established tumors that can be detected by ultrasonography and for which surgery is already standardized, patients with medullary thyroid carcinomas larger than 10 mm in greatest dimension and tumors with distant metastases (M1) were excluded. Because of these stipulations, only patients with normal histopathological findings on examination of the thyroid, C-cell hyperplasia, or medullary thyroid carcinomas without distant metastases were enrolled, creating a homogeneous study population.

Data were collected with the use of a standardized questionnaire with patient identifiers removed in order to comply with national data-protection and confidentiality regulations. Data were collected on the genotype and phenotype of individual patients and their families, patients' age at surgery, the type of surgery performed, surgical histopathological findings, and postoperative serum calcitonin levels.

Approval by the various institutional review boards was waived, since all clinical interventions represented the standard practice of care and since prophylactic thyroidectomy based solely on a positive genetic test had become the gold standard of care at the inception of the study.^{13,14} Because of the high rates of response from the central European countries (Germany, 109 patients; France, 61; the Netherlands, 14; Italy, 11; Austria, 5; Great Britain, 5; and Norway, 2), the study sample was largely drawn from central Europe. To account for the low incidence of RET mutations (1 carrier per 500,000

population),¹⁵ the recruitment period was extended from July 7, 1993 (when the first prophylactic thyroidectomy was performed in an asymptomatic carrier of a RET gene mutation on the basis of genetic evidence), to February 28, 2001. All expenditures incurred within the study, if not covered by national health insurance plans, were defrayed by institutional budgets.

GENETIC TESTING

Before undergoing screening and genetic testing, all patients or their parents or legal guardians gave written informed consent in accordance with institutional guidelines and national regulations that have their origin in the Declaration of Helsinki. For the identification of germ-line mutations in RET, genomic DNA was purified from peripheral-blood leukocytes with the use of standard techniques. Genomic DNA was amplified by the polymerase chain reaction with the use of oligonucleotide primers for exons 10, 11, 13, 14, 15, and 16. Single-strand conformation polymorphism analysis and direct sequencing were performed according to national laboratory regulations for RET analysis.

PROPHYLACTIC THYROIDECTOMY AND LYMPH-NODE DISSECTION

All 207 study patients underwent a standard total thyroidectomy (an inclusion criterion), and all patients or their parents or guardians gave written informed consent beforehand. Since there is no consensus about the need for additional prophylactic lymph-node dissection in asymptomatic carriers of RET gene mutations when no tumors or nodal metastases are visible on preoperative imaging,⁶ systematic lymph-node dissection was not mandatory. In conjunction with total thyroidectomy, 148 of the 207 patients (71.5 percent) nonetheless underwent prophylactic dissection of the central lymph-node compartment, which extends vertically from the hyoid bone to the thoracic inlet and horizontally between the carotid sheaths. All patients who either did not undergo central lymph-node dissection or had no evidence of lymph-node metastasis on pathological examination were assumed to be free from lymph-node metastasis if their serum calcitonin levels returned to normal postoperatively.

PATHOLOGICAL EXAMINATION AND TUMOR STAGING

After gross evaluation by the pathologist at each patient's hospital, who was aware only of the patient's

status as a carrier of a RET mutation, the entire thyroid gland was divided vertically to separate the left and right lobes. The thyroid halves were then sectioned horizontally from the superior to the inferior pole. After fixation in formalin, the whole thyroid gland was embedded in paraffin. Soft tissue and lymph nodes were processed separately. Conventional staining with hematoxylin and eosin and calcitonin immunohistochemical analysis involving a standard immunoperoxidase technique were used throughout. A diagnosis of medullary thyroid carcinoma was based on evidence of extension beyond the basement membrane, demonstration of lymphatic or vascular invasion on histopathological analysis, or both findings. C-cell hyperplasia was diagnosed by the hospital pathologist when each low-power field showed more than 50 intrafollicular calcitonin-positive cells, more than 6 C cells per thyroid follicle, or both. Tumor staging was performed according to the International Union against Cancer tumor-node-metastasis (TNM) classification.

STATISTICAL ANALYSIS

Associations between categorical variables were evaluated with use of the two-tailed Fisher's exact test.¹⁶ To analyze differences in patients' ages among the pathological subgroups, we used one-way analysis of variance.¹⁷ Each analysis of variance was followed by post hoc tests for simultaneous pairwise comparisons of factor levels (that is, categories of pathological thyroid findings and subgroups of germ-line mutations in RET codon 634, respectively). P values were adjusted for multiple tests of factor levels according to the Tukey-Kramer test.¹⁸ All P values were two-tailed.

RESULTS

SPECIFIC RET MUTATIONS

Of the 207 patients enrolled, 98 were male and 109 female. These 207 patients belonged to 145 families; 29 families had the familial medullary thyroid carcinoma phenotype, and 112 the MEN-2A phenotype. The MEN-2B mutations in the remaining four families were all spontaneous. The histologic findings in the thyroid included normal architecture in 11 patients (5.3 percent), C-cell hyperplasia in 66 patients (31.9 percent), medullary thyroid carcinomas without nodal metastases in 123 patients (59.4 percent), and medullary thyroid carcinoma with nodal metastases in 7 patients (3.4 percent). Among the 207 patients (Table 1), the most commonly mu-

Table 1. Specific RET Mutations Associated with Multiple Endocrine Neoplasia and Variants.

RET Mutation	Affected Exon	Affected Codon	Mutation		Patient-Based Frequency (N=207)	Family-Based Frequency (N=145)
			Nucleotide	Amino Acid		
C609R	10	609	TGC→CGC	Cys→Arg	4 (1.9)	1 (0.7)
C611Y	10	611	TGC→TAC	Cys→Tyr	4 (1.9)	4 (2.8)
C618					19 (9.2)	10 (6.9)
C618F	10	618	TGC→TTC	Cys→Phe	1 (0.5)	1 (0.7)
C618G	10	618	TGC→GGC	Cys→Gly	4 (1.9)	1 (0.7)
C618R	10	618	TGC→CGC	Cys→Arg	6 (2.9)	2 (1.4)
C618S	10	618	TGC→AGC/TCC	Cys→Ser	7 (3.4)	5 (3.4)
C618Y	10	618	TGC→TAC	Cys→Tyr	1 (0.5)	1 (0.7)
C620					14 (6.8)	10 (6.9)
C620F	10	620	TGC→TTC	Cys→Phe	1 (0.5)	1 (0.7)
C620R	10	620	TGC→CGC	Cys→Arg	8 (3.9)	6 (4.1)
C620S	10	620	TGC→AGC/TCC	Cys→Ser	3 (1.4)	2 (1.4)
C620Y	10	620	TGC→TAC	Cys→Tyr	2 (1.0)	1 (0.7)
C630R	11	630	TGC→CGC	Cys→Arg	1 (0.5)	1 (0.7)
C634					130 (62.8)	98 (67.6)
C634F	11	634	TGC→TTC	Cys→Phe	10 (4.8)	7 (4.8)
C634G	11	634	TGC→GGC	Cys→Gly	6 (2.9)	5 (3.4)
C634R	11	634	TGC→CGC	Cys→Arg	54 (26.1)	41 (28.3)
C634S	11	634	TGC→AGC/TCC	Cys→Ser	10 (4.8)	6 (4.1)
C634W	11	634	TGC→TGG	Cys→Trp	6 (2.9)	5 (3.4)
C634Y	11	634	TGC→TAC	Cys→Tyr	44 (21.3)	34 (23.4)
E768D	13	768	GAG→GAC	Glu→Asp	2 (1.0)	1 (0.7)
L790F	13	790	TTG→TTC/TTT	Leu→Phe	14 (6.8)	7 (4.8)
Y791F	13	791	TAT→TTT	Tyr→Phe	5 (2.4)	3 (2.1)
V804M	14	804	GTG→ATG	Val→Met	4 (1.9)	3 (2.1)
S891A	15	891	TCG→GCG	Ser→Ala	6 (2.9)	3 (2.1)
M918T	16	918	ATG→ACG	Met→Thr	4 (1.9)	4 (2.8)

tated RET codon was 634 (62.8 percent), followed by codon 618 (9.2 percent); codons 620 and 790 (6.8 percent each); codon 891 (2.9 percent); codon 791 (2.4 percent); codons 609, 611, 804, and 918 (1.9 percent each); codon 768 (1.0 percent); and codon 630 (0.5 percent). Patient-based frequencies of each of the 12 mutated RET codons were similar to the family-based frequencies. The patient-based frequencies of individual genotypes within the extracellular-domain codons 618, 620, and 634 ranged from 0.5 to 4.8 percent, except in the case of the more common C634Y and C634R genotypes, which had a respective frequency of 21.3 and 26.1 percent.

AGE-RELATED PROGRESSION TO MEDULLARY THYROID CARCINOMA

There was a significant age-related progression from C-cell hyperplasia to medullary thyroid carcinoma and, ultimately, nodal metastasis in patients whose RET mutations were grouped according to the extracellular- and intracellular-domain codons affected (Table 2). The mean age at diagnosis was 8.3 years among patients with C-cell hyperplasia and extracellular-domain mutations and 11.2 years among such patients with intracellular-domain mutations (P=0.01). Among patients with node-negative medullary thyroid carcinoma, the mean age at diagnosis was 10.2 years in those with extracellular-domain mutations and 16.6 years in those with intracellular-domain mutations (P=0.002). Among patients with node-positive medullary thyroid carcinoma, the mean age at diagnosis was 17.1 years in those with extracellular-domain mutations. None of the eight patients with medullary thyroid carcinoma and intracellular-domain mutations had nodal metastases during the first two decades of life. The

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Table 2. Progression to Medullary Thyroid Carcinoma in the First Two Decades of Life, According to the Position of the RET Codon Domain.*

Thyroid Pathological Findings	No. of Patients†	Mean Age (95% CI) yr	Sequence of Progression	Mean Change in Age (95% CI) yr	P Value	
					Pairwise‡	Overall§
Extracellular-domain codons¶	172					<0.001
Normal	7	10.0 (6.7 to 13.3)	Progression to C-cell hyperplasia	-1.7 (-5.2 to 1.8)	0.77	
C-cell hyperplasia	47	8.3 (7.0 to 9.6)	Progression to medullary thyroid carcinoma N0	1.9 (0.4 to 3.4)	0.07	
Medullary thyroid carcinoma						
N0	111	10.2 (9.3 to 11.0)	Progression to N1	6.9 (3.6 to 10.3)	<0.001	
N1	7	17.1 (13.9 to 20.4)	—	—	—	
Intracellular-domain codons 	31					0.005
Normal	4	9.0 (4.8 to 13.2)	Progression to C-cell hyperplasia	2.2 (-2.4 to 6.8)	0.59	
C-cell hyperplasia	19	11.2 (9.3 to 13.1)	Progression to medullary thyroid carcinoma N0	5.4 (1.9 to 8.9)	0.01	
Medullary thyroid carcinoma						
N0	8	16.6 (13.7 to 19.6)	Progression to N1	—	—	
N1	0	—	—	—	—	

* CI denotes confidence interval, N0 no nodal involvement, and N1 nodal involvement.

† Four carriers of the M918T genotype who had node-negative medullary thyroid carcinoma were excluded.

‡ P values were adjusted for all pairwise comparisons within one factor according to the Tukey-Kramer test¹⁸ (adjacent pathological groups).

§ Overall the P values were calculated with the use of one-way analysis of variance.

¶ Extracellular-domain codons are 609, 611, 618, 620, 630, and 634.

|| Intracellular-domain codons are 768, 790, 791, 804, and 891.

mean age at diagnosis did not differ significantly between those who had normal thyroid histological findings and those who had C-cell hyperplasia, possibly reflecting how difficult it is for a pathologist to distinguish reliably between normal thyroid histopathological findings and C-cell hyperplasia.

Grouping the rare RET mutations as extracellular- and intracellular-domain mutations is not a useful way of identifying the optimal age at which asymptomatic carriers of these mutations should undergo prophylactic thyroidectomy. As more clinical information emerges, some of the rare RET mutations may need to be reclassified if they turn out to behave differently from others in that group. For the purposes of statistical analysis, the numbers of patients were adequate for analysis only among those with codon 634 mutations. In this subgroup, the mean age of the patients at progression was 6.9

years for C-cell hyperplasia, 10.1 years for node-negative medullary thyroid carcinoma, and 16.7 years for node-positive medullary thyroid carcinoma (Table 3). The type of amino acid substitution had no significant effect on the age-related penetrance of codon 634 mutations.

CUMULATIVE AGE-RELATED RISK AMONG PATIENTS WITH THE CODON 634 GENOTYPE

Among the patients with the codon 634 genotype (Fig. 1), malignant transformation was present as early as one year of age. The cumulative age-related risk of medullary thyroid carcinoma increased progressively with age, but there was no pathological evidence of spread to the lymph nodes before the age of 14 years. Twelve of 16 carriers (75.0 percent) of codon 634 germ-line mutations who were younger than five years of age at the time of prophylactic

Table 3. Progression to Medullary Thyroid Carcinoma in the First Two Decades of Life among Carriers of Codon 634 RET Germ-Line Mutations.*

Thyroid Pathological Findings	C634R Mutation		C634Y Mutation		C634F, C634G, C634S, or C634W Mutation†		P Value‡
	No. of Patients	Mean Age (95% CI) yr	No. of Patients	Mean Age (95% CI) yr	No. of Patients	Mean Age (95% CI) yr	
C-cell hyperplasia	8	6.9 (4.8–9.0)	8	6.0 (3.9–8.1)	5	8.2 (5.5–10.9)	0.42
Medullary thyroid carcinoma							
N0	43	9.7 (8.3–11.1)	33	10.7 (9.0–12.3)	26	10.0 (8.1–11.8)	0.65
N1	3	16.3 (12.2–20.5)	3	17.0 (12.9–21.1)	0	—	0.77
			Sequence of Progression				P Value
		Mean Age (95% CI) yr		Mean Age (95% CI) yr			Pairwise§
All codon 634 mutations†							Overall‡
C-cell hyperplasia	21	6.9 (4.9–8.8)	Progression to medullary thyroid carcinoma N0	3.2 (1.2–5.4)			0.008
Medullary thyroid carcinoma							
N0	102	10.1 (9.2–11.0)	Progression to N1	6.6 (2.8–10.3)			0.002
N1	6	16.7 (13.1–20.4)	—	—			—

* CI denotes confidence interval, N0 no nodal involvement, and N1 nodal involvement.

† One patient with normal findings was excluded from the analysis.

‡ The P values were calculated with the use of one-way analysis of variance.

§ P values were adjusted for all pairwise comparisons within one factor according to the Tukey–Kramer test¹⁸ (adjacent pathological subgroups).

thyroidectomy had node-negative medullary thyroid carcinomas. The cumulative age-related risk of nodal metastasis rose steadily from 14 years of age, reaching 42 percent at the age of 20 years (Fig. 1). Four patients (13, 16, 19, and 20 years of age) had stimulated calcitonin values that remained abnormal postoperatively, indicating residual nodal or distant metastasis. All four patients had codon 634 germ-line mutations, with two patients each harboring the C634R and C634Y genotypes. At surgery, three of these four patients had nodal metastases in the central cervical lymph-node compartment. The fourth did not undergo lymph-node dissection.

AGE-RELATED PENETRANCE OF THE RET GENOTYPES

The age-related differences in tumor penetrance among the RET mutations apparently apply also to other tissues of neural-crest derivation (Table 4^{11,19–32}): the higher the RET risk category, the higher the corresponding rates of familial MEN phenotypes — that is, the more frequent the involvement of parathyroid and adrenal tissues in these families. Pheochromocytomas developed concomitantly in 3 of the 207 study patients (1.4 percent) (they were

unilateral in 2 patients and unspecified in 1 patient). These patients were 12, 14, and 20 years of age at the time of prophylactic thyroidectomy, and all had RET mutations in codon 634. Conversely, no patient with hyperparathyroidism was identified. However, some specimens from suspicious-appearing parathyroid glands that had been obtained by tissue biopsy or resection at the surgeon's discretion did exhibit early histopathological features of parathyroid adenoma.

DISCUSSION

Hereditary medullary thyroid carcinoma evolves from preneoplastic C-cell hyperplasia.³² The term “C-cell hyperplasia” may be a misnomer because the cytologic atypia is recognizable on routine staining with hematoxylin and eosin.³³ Neoplastic transformation from C-cell hyperplasia to medullary thyroid carcinoma is a qualitative, not a quantitative, change.³³ The use of numerical criteria may thus be irrelevant for the diagnosis.³³ The concordant monoclonal patterns of C-cell hyperplasia found in both thyroid lobes of carriers of a germ-line C634Y RET mutation support the concept that early

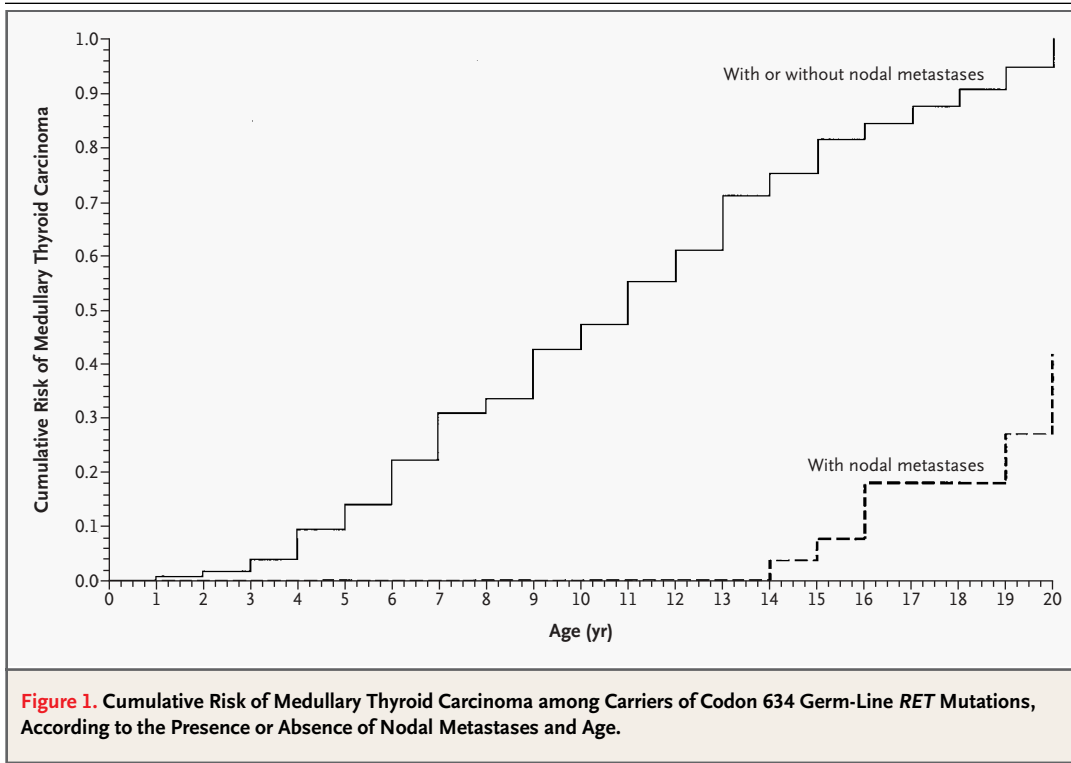


Figure 1. Cumulative Risk of Medullary Thyroid Carcinoma among Carriers of Codon 634 Germ-Line *RET* Mutations, According to the Presence or Absence of Nodal Metastases and Age.

clonal expansion precedes the divergence of C-cell precursors of each thyroid lobe.³⁴ There is a characteristic lag between phases — from the transformation from neoplastic C-cell hyperplasia to medullary thyroid carcinoma, and from carcinoma to the spread of tumor cells to lymph nodes. Among patients with the codon 634 genotype, the average interval from tumor development to nodal metastasis was 6.6 years — a time span that could allow timely surgical intervention in known carriers.

Hereditary medullary thyroid carcinoma is a good model with which to evaluate the usefulness of interventional therapy in patients who have a genetic predisposition to cancer. Barring human error, the use of DNA-based predictive testing for *RET* germ-line mutations involving exons 10, 11, 13, 14, 15, and 16 permits a precise genetic diagnosis to be made, avoiding the false positive and false negative calcitonin-test results.⁴ The medical benefits of genetic testing followed by prophylactic thyroidectomy should virtually eliminate the risk of medullary thyroid carcinoma³⁵ and should far outweigh the transient psychological distress that is typical among carriers of *RET* mutations during the first year after genetic test results have been reported.³⁶ Although frequent follow-up for disease might seem

unnecessary in carriers of *RET* mutations who have C-cell hyperplasia or normal histopathological findings in surgical specimens of the thyroid, no conclusions can be drawn until long-term results become available. Genetic testing does not obviate the need for biochemical studies to detect pheochromocytoma or hyperparathyroidism in these patients. Concomitant adrenal and parathyroid tumors occur in 50 percent and 10 percent of patients, respectively.²⁶ *RET* screening before symptoms develop cannot identify spontaneous mutations that have not yet occurred. These spontaneous mutations mainly involve codons 918 and 634 and accounted for 5.6 percent of *RET* germ-line mutations in the French MEN Register.³⁷

Perhaps the most important question related to genetic testing is when to perform total thyroidectomy in a carrier of a *RET* gene mutation. Early prophylactic thyroidectomy will most likely obviate the need for the potentially more radical approach to medullary thyroid carcinoma, which requires systematic dissection of the central cervical lymph-node compartment.²⁶ The clinical phenotypes associated with specific variants of hereditary medullary thyroid carcinoma suggest that any approach should take into account the transforming potential of the

Table 4. Genotypic Testing for RET Mutations and Clinical Implications.

Affected Codon	No. of Patients	Earliest Age at Presentation of Medullary Thyroid Cancer		Positive for Familial MEN Phenotype*
		Current Study	Other Studies	
				%
918	4	9 mo	13 mo ¹⁹	100†
634	130	15 mo	17 mo ²⁰	95
618	19	7 yr	7 yr ^{11,21}	80
611	4	7 yr	20 yr ²²	50
620	14	11 yr	12 yr ²³	40
790	14	12 yr	12 yr ¹¹	14
891	6	13 yr	48 yr ²⁴	0
630	1	15 yr	34 yr ²⁵	100
804	4	20 yr	6 yr ^{26,27}	0
609	4	>20 yr	5 yr ²⁸	100
791	5	>20 yr	21 yr ²⁹	67
768	2	>20 yr	22 yr ³⁰⁻³²	0

* MEN denotes multiple endocrine neoplasia.

† These four patients had the MEN type 2B phenotype.

respective RET mutation. Because the transforming potential of the mutations in the same extracellular-domain codon of the RET gene is similar in vitro³⁸ and in vivo, patients with specific genotypes can be grouped according to their extracellular-domain codon mutations regardless of the specific amino acid substitution in the respective codon.

The 1999 consensus statement⁶ of the Seventh International Workshop on Multiple Endocrine Neoplasia advocates prophylactic total thyroidectomy before the age of five years in patients with mutations in RET codon 611, 618, 620, or 634. The participants in this workshop, most of whom were clinical endocrinologists, failed to reach agreement on the approach to children with codon 609, 768, 790, 791, 804, or 891 mutations; the recommended age for prophylactic total thyroidectomy ranged

from 5 to 10 years. No consensus was reached on the need for prophylactic dissection of the central cervical lymph-node compartment.⁶

Although the prognostic scope of our study is limited because of the short follow-up period, our data provide additional information. In asymptomatic carriers of germ-line mutations in RET codon 634, malignant progression from C-cell hyperplasia to medullary thyroid carcinoma may occur during the first years of life. Once malignant transformation has taken place, nodal metastasis occurs an average of 6.6 years later. None of the asymptomatic carriers of mutations in codon 611, 618, or 620 had evidence of medullary thyroid carcinoma before the age of five years. Though limited because of the small numbers of patients, our data do not suggest a need for prophylactic thyroidectomy in asymptomatic carriers of mutations in codon 609, 630, 768, 790, 791, 804, or 891 before the age of 10 years or for central lymph-node dissection before the age of 20 years.

Owing to the unpredictability of the timing of somatic “hits” required for malignant progression, there may be a small risk of earlier progression to medullary thyroid carcinoma beyond that delineated by our data. For example, metastatic medullary thyroid carcinoma developed in a six-year-old girl who had the V804M germ-line mutation in RET.^{26,27} The benefit of the cure offered by prophylactic thyroidectomy will be offset by the potential overtreatment of some carriers of RET mutations, owing to the variation in the expression and penetrance of these mutations, such as those affecting codons 611, 790, 791, and 804.^{22,39,40}

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APPENDIX

In addition to the authors, the following investigators participated in the EUROMEN study (in descending order according to the number of patients enrolled): Universität Wien, Vienna, Austria — B. Niederle; Università degli Studi di Ferrara, Ferrara, Italy — G. Pansini; St. Marien-Hospital, Lünen, Germany — G. Görtz; Università di Firenze, Florence, Italy — M.-L. Brandi, R. Gheri; Klinikum Buch, Berlin, Germany — D. Geipel; Westfal-Klinikum, Kaiserslautern, Germany — B. Koch; Università degli Studi di Pisa, Pisa, Italy — P. Miccoli; Royal Victoria Hospital, Belfast, Northern Ireland — C. Russel; Johann-Gutenberg-Universität, Mainz, Germany — S. Walgenbach; Bristol Royal Infirmary, University of Bristol, Bristol, United Kingdom — J. Farndon; Universität Rostock, Rostock, Germany — R. Hampel; Zentralkrankenhaus Augsburg, Augsburg, Germany — A. Heiss; Haukeland Sykehus, Universitetet i Bergen, Bergen, Norway — J. Varhaug; Diakonissenkrankenhaus, Stuttgart, Germany — R. Ernst; Gemeinschaftspraxis, Stuttgart, Germany — C. Hartenstein; Martin-Luther-Universität Halle-Wittenberg, Halle (Saale), Germany — U. Schneyer.

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