Rare RET Variant p.D707E in a Chinese Pedigree with Hereditary Medullary Thyroid Carcinoma

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Key Words

Hereditary medullary thyroid carcinoma · RET proto-oncogene · Variant · Single-nucleotide polymorphism

Abstract

Background: Hereditary medullary thyroid carcinoma (HMTc) is thought to be associated with germline mutations of the RET proto-oncogene. **Methods:** We detected RET proto-oncogene germline mutations from a pedigree with HMTc in the east of China and investigated the characteristics of these mutations in this pedigree and their correlation with HMTc by direct sequencing of all 21 exons in the RET gene of all 46 subjects. **Results and Conclusion:** (1) Thirteen types of RET gene variants were detected in this pedigree. Of these, p.F285S in exon 4, c.854_855CA in exon 4,

and p.D707E in exon 11 are reported for the first time in our study. (2) Both linkage disequilibrium analysis and logistic regression analysis showed a significant correlation between the p.D707E variant and HMTc (LOD = 3.69, OR = 4.413, $p = 0.000167$), indicating that this variant is a risk factor for medullary thyroid carcinoma (MTC). (3) The single-nucleotide polymorphisms (SNP) G691S in exon 11 (rs1799939), S904S in exon 15 (rs1800863), and rs2075912 and rs2565200 in the 3'-untranslated region of the RET proto-oncogene are in complete linkage disequilibrium ($D' = 1$, $r^2 = 1$); no correlation of these SNP and MTC was observed in this pedigree. (4) No hot-spot mutation of the RET proto-oncogene was detected in this pedigree. We drew the conclusion that the heterozygous nonsynonymous variant p.D707E in the RET proto-oncogene is rare, but it is a risk factor for hereditary MTC.

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Introduction

Medullary thyroid carcinoma (MTC) is a rare aggressive endocrine tumor that arises from parafollicular C cells that produce calcitonin, and it accounts for 5–10% of all thyroid cancers. About 75% of all MTC are sporadic forms, while 25% are hereditary MTC (HMTc) [1–3]. HMTc is an autosomal dominant genetic disease with 3 subtypes: multiple endocrine neoplasia type 2A (MEN 2A; 55–60%), multiple endocrine neoplasia type 2B (MEN 2B; 5–10%) and familial MTC (35–40%). MEN 2A is generally accompanied by adrenal pheochromocytoma (PHEO) and/or hyperparathyroidism, and the onset age usually ranges from 20 to 30 years [3–5].

The pathogenesis of MTC is thought to be associated with mutations of the RET proto-oncogene (RET, OMIM.164761), which is mapped on chromosome 10q11.2 and contains 21 exons encoding a membrane tyrosine kinase receptor that mediates the processes of neural crest-derived cells, such as proliferation, differentiation, and migration. The probability of carriers with germline mutations of this gene to develop HMTc is about 90% [6–8]. Half of these patients' first-degree relatives seem to be at risk for carrying the mutated gene [9]. In the inherited cases about 98% of the patients harbor germline mutations in this gene, and in the sporadic cases approximately 45% of the patients carry somatic mutations [10–12]. HMTc is generally associated with RET proto-oncogene germline mutations, which are frequently distributed in hot-spot exons (i.e. 5, 8, 10, 11, 13, 14, 15, and 16) mainly affecting the 2 domains of RET: the extracellular cysteine-rich (ECR) region and the intracellular tyrosine-kinase (ITK) domain. Mutations in these 2 domains may result in changes in protein conformation in the extracellular domain and the intracellular domain, respectively. These changes in protein conformation could enhance the transforming ability of RET, automatically stimulating tyrosine kinase phosphorylation, inducing excessive cell hyperplasia, and eventually leading to a tumor. Therefore, these 2 domains play an important role in the development of MTC [13, 14].

Herein, we detect RET proto-oncogene germline mutations in a pedigree with HMTc to understand the characteristics of these mutations. RET gene screening could be essential for the prevention of MTC and to facilitate the proper clinical management of MTC patients.

Table 1. Primers used for PCR amplification

Exon	F/R	Primers (5'-3')	Size, bp	Temperature, °C
1	1F	TCTCTACTACCCCAGGATGC	1,316	61.2
	1R	CAGAACTCTCCGCACGAATC		65.1
2	2F	TGTCCTTGAAGAAGCCTTAT	400	59
	2R	GTGTCAGCGGCTGTGATAAG		63.5
3	3F	CCCCACAGACCTGACTTCTC	400	63.5
	3R	AACCAGATGGCTTGTGTCAA		63
4	4F	CAAACCTCGTAAGCACAGTCA	439	58.8
	4R	CTTCCGCTTGAAGTCCACCA		68
5	5F	ACGTGCAGCATTCTAAGGTC	367	62.4
	5R	TGTGTGTAGGGTGCTGCTTG		64.6
6	6F	GTGTCTGGGAAGAGGTGTGC	315	64.3
	6R	TCAATCTTCCCCAGACAGGC		66.8
7	7F	TTCCAGGACTTAGGCTGTGT	503	61.7
	7R	TTACTGCTGGGTCACTCAGG		62.8
8	8F	GCTGGTGCTGTTCCCTGTCC	446	69.6
	8R	CCTTCCCAAGTCCAGAGTGA		64.2
9	9F	TCCAGTTGCTCCTCCCTAGA	239	64.3
	9R	CCATGCCCTGATTAAACCCT		66.3
10	10F	CACCCATGGCTTCAGAAAGG	375	67.4
	10R	TGTGCTGTTGAGACCTCTGT		60
11	11F	CATGAGGCAGAGCATACGCA	512	67.5
	11R	CCCACAGACTGTCCCCACAC		67.3
12	12F	TCCTCCCCTGTCATCCTCAC	305	66.2
	12R	GCTCTTCAGGGTCCCATGCT		68.5
13	13F	GTCTTTGCAGGCCTCTCTGT	301	63.8
	13R	GAGAACAGGGCTGTATGGAG		61.5
14	14F	GCTGTGTCCACCCCTTACT	452	65.9
	14R	TAGAGTGTGGCATGGTGGGG		68.3
15	15F	TGGGCGACCTCATCTCATT	604	65.9
	15R	CTAGGCTTCCCAAGGGCACT		66.3
16	16F	GCCTGGCCTTCTCCTTTACC	184	66.1
	16R	GTAACCTCCACCCCAAGAGA		63.3
17	17F	GACATCTGTGAGCATCTGTG	328	57.6
	17R	CACAGATGTCCCCTCCCTTC		65.9
18	18F	GGCCCTGCTTGGATCATATT	218	64.8
	18R	AACTACTGCCCTGGGGTGAG		63.3
19-1	19-1F	TCTAGTTGTGGCACATGGCT	595	55.1
	19-1R	GGCTCCTTCTCAACTGAAT		58.5
19-2	19-2F	AAATATACAAATCTGGGGAG	502	56.1
	19-2R	GGAACCGTCTCAGCTTGAAA		64.8
20	20F	TCTAGTTGTGGCACATGGCT	244	63.3
	20R	CGGTGCTAGAATCTAGTAAA		55.1
21-1	21-1F	GAGTTTGGCCAAAGGCCTTAC	825	64.1
	21-1R	TCTCAAGATCTCGAATGCTG		60.4
21-2	21-2F	GCCTGGGGGTAGTGTCAATG	798	67.1
	21-2R	GAGACTTCCCAAAAGCTGCC		66.1
21-3	21-3F	TTGTCATTCTTCATTGCTTG	986	58.8
	21-3R	ATGCCTCAGTGGTTATCATG		60

F = Forward; R = reverse.

Subjects and Methods

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

A 5-generation Chinese Han pedigree with HMTc from Shandong Province, China, was investigated. All 46 subjects provided written informed consent for participation in this study, as required by the Medical Ethics Committee of the School of Public Health of Xiamen University.

Genomic DNA was isolated from EDTA anti-coagulated peripheral blood (5 ml) of all subjects. Leukocytes were isolated using the standard salting out/proteinase K method, dissolved in TE buffer, and stored at -20°C.

All primers were designed using Oligo 6.0 software (NCBI reference sequence: NG_007489.1) and synthesized by Sangon Biotech (Shanghai, China) (table 1). Because exons 19 and 21 are too long, they were divided into 2 pairs of primers (i.e. 19-1 and 19-2) and 3 pairs of primers (i.e. 21-1, 21-2, and 21-3), respectively.

Polymerase chain reaction amplification was performed for all 21 exons in the RET gene, and the samples were then run on a 2% agarose gel. The polymerase chain reaction products were purified and sequenced using an ABI Prism 3130X automatic sequencer (Applied Biosystems, USA). The sequences were compared with

RET sequence data from the NCBI BLAST human database (<http://www.ncbi.nlm.nih.gov/BLAST/>), the UCSC Genome Browser (<http://genome.ucsc.edu/cgi-bin/hgBlat>), and the ExAC Browser (<http://exac.broadinstitute.org/>), respectively.

Statistical Analysis

Linkage disequilibrium was analyzed using the R package paramlink. LOD scores >3 indicated a linkage between the variant and the disease. LOD scores ≤2 indicated no linkage between the variant and the disease. SPSS 17.0 (SPSS Inc., Chicago, Ill., USA) was used for logistic regression analysis to determine whether these 13 types of variants are risk factors for HMTc.

Results

Basic Characteristics of the Subjects

A total of 46 participants were included in this study (24 females and 22 males, female:male ratio: 1.09:1, age range: 3–83 years). Of these, 8 patients (age range: 26–83 years) had MTC alone, 5 patients (age range: 29–54 years) had MTC accompanied by PHEO, and the remaining 33 patients were the unaffected relatives of these patients. The basic characteristics of the 46 subjects are listed in table 2. Information about the phenotype, the age at the onset of MTC and PHEO, and the age at surgery for MTC and PHEO is listed in table 3. The age at the onset of MTC ranged from 18 to 50 years, and family members III-5 and III-18 presented recurrence of MTC after surgical treatment for the first time. The age at the onset of PHEO ranged from 26 to 50 years. We provide a representative sample of histology images of tumor tissue from a patient with HMTc in this pedigree. The results of hematoxylin-

Table 2. Basic characteristics of the 46 subjects

	MTC only	MTC+ PHEO	Normal	Total
Females, n	5	3	16	24
Males, n	3	2	17	22
Female:male ratio	1.67:1	1.50:1	0.94:1	1.09:1
Age range, years	26–83	29–54	3–70	3–83

Table 3. Basic characteristics of the 13 patients

Subject	Gender	Age, years	Phenotype	Age at onset of MTC, years	Age at surgery for MTC, years	Age at onset of PHEO, years	Age at surgery for PHEO, years
III-2	F	52	MTC+PHEO	18	18	37 (bilateral)	42
III-3	M	83	MTC only	–	–		
III-5	M	71	MTC only	46	46 and 50		
III-8	F	48	MTC only	–	–		
III-11	M	48	MTC+PHEO	45	47	46 (bilateral)	47
III-14	F	54	MTC+PHEO	50	51	50 (bilateral)	51
III-18	F	65	MTC only	33	33 and 62		
III-19	M	50	MTC+PHEO	47	47	48 (left)	48
III-25	M	54	MTC only	–	–		
IV-2	F	29	MTC+PHEO	26	26	26 (bilateral)	26
IV-3	F	26	MTC only	–	–		
IV-5	F	27	MTC only	23	23		
IV-15	F	28	MTC only	18	25		

– = Lack of information; M = male; F = female.

eosin (HE) staining and immunohistochemical staining [calcitonin (CT), chromogranin A (CgA), synaptophysin (Syn), carcinoembryonic antigen (CEA), S100, and thyroglobulin (TG)] were in accordance with the diagnosis of MTC. Tumor cells in HE staining were round, polygonal, and spindle shaped, and the nucleus was lightly stained; the ratio of nucleus to cytoplasm was low, and the

tumor cells were arranged in nests, with pink dense amyloids around the cells. Staining for CT, CgA, CEA, and Syn showed a positive expression in the cytoplasm of tumor cells and a negative expression in thyroid follicular epithelial cells. TG showed a negative expression in tumor cells, while its expression in the thyroid follicular epithelial cytoplasm was strongly positive. Immunohisto-

Fig. 1. Immunohistochemical staining of a representative HMTc patient in this pedigree. HE. $\times 100$. The tumor cells are arranged in nests, with pink dense amyloids around the cells. The expressions of CT, CgA, Syn, and CEA are positive ($\times 200$). The expressions of S100 and TG are negative in tumor cells ($\times 100$).

Table 4. Distribution of the 13 types of variants in the RET gene

Region	Position	SNP ID	RET mutation	Total, n	Female to male ratio	Patient to normal subject ratio	Homozygous to heterozygous ratio	LOD score (MTC)	p	LOD score (PHEO)	p
Exon 2	43595968	rs1800858	p.A45A	45	23:22	13:32	42:3	NA	0.995	NA	0.995
Exon 4	43600628	–	p.F285S	7	3:4	1:6	7:0	NA	0.451	NA	0.575
Exon 4	43600628–43600629	–	C.854_855CA	9	6:3	3:6	9:0	NA	0.583	NA	0.137
Exon 7	43606687	rs1800860	p.A432A	45	23:22	13:32	27:18	0.22	NA	0.00	NA
Exon 11	43610119	rs1799939	p.G691S	1	1:0	0:1	1:0	NA	0.995	NA	0.995
Exon 11	43610169	–	p.D707E	15	8:7	11:4	15:0	3.69 ^a	0.0002	0.39	0.995
Exon 13	43613843	rs1800861	p.L769L	23	13:10	4:19	0:23	0.28	0.186	0.00	1.000
Exon 13	43613868	rs75686697	p.V778I	7	6:1	0:7	0:7	0.70	0.994	0.00	0.995
Exon 15	43615633	rs1800863	p.S904S	13	9:4	1:12	0:13	0.22	0.105	0.00	0.995
3'-UTR	43622217	rs2075912	C.*15T>C	44	23:21	13:31	22:22				
3'-UTR	43622369	rs2075913	C.*167T>A	37	19:18	8:29	12:25				
3'-UTR	43622933	rs2565200	C.*731T>C	43	22:21	13:30	21:22				
3'-UTR	43625223	rs2742241	C.*1506G>A	39	21:18	11:28	17:22				

– = No related information was found in the NCBI BLAST human database, the UCSC Genome Browser, or the ExAC Browser; NA = not applicable; p = probability from the logistic regression analysis. ^a LOD scores >3 were considered to determine a linkage between the variant and the disease.

chemical staining of S100 presented a negative expression in both tumor cells and thyroid follicular epithelial cells (fig. 1). The HMTC cases found in our study did not have distinct histologic features compared to MTC tumors with other types of RET mutations.

RET Proto-Oncogene Germline Mutation Detection and Variation Annotation

The results of mutation detection showed 13 types of germline variants in the 21 exons of the RET proto-oncogene. They were: p.A45A in exon 2, p.F285S and c.854_855CA in exon 4, p.A432A in exon 7, p.D707E and p.G691S in exon 11, p.L769L and p.V778I in exon 13, p.S904S in exon 15, and c.*15T>C, c.*167T>A, c.*731T>C, and c.*1506G>A in the 3'-untranslated region (3'-UTR). Among the 13 variants, no information on p.F285S and c.854_855CA in exon 4 or p.D707E in exon 11 was found in the NCBI, UCSC, and ExAC databases, suggesting that these 3 variants have not yet been reported. Of the remaining 10 variants, single-nucleotide polymorphisms (SNP) such as p.A45A, p.A432A, p.G691S, and p.L769L were confirmed to be related to C-cell hyperplasia, sporadic MTC, papillary thyroid carcinoma, and Hirschsprung's disease in some populations [5, 15–18]. However, no correlation was found between these variants and MTC/PHEO in this pedigree.

Among the 13 types of variants in this pedigree, patients with MTC alone and those with MTC accompanied by PHEO carried 11 types of variants, while the other 2 variants, i.e. p.G691S and p.V778I, were not found in any of the MTC patients. We analyzed the prevalence of the 11 variants of mutation carriers. Among these, the prevalence of p.D707E mutation carriers was highest (i.e. 73.33%; 11/15) (table 5).

Familial MTC pedigrees harbor hot-spot mutations such as codons 609, 611, 618, and 620 in exon 10 and codon 634 in exon 11 (the most frequent mutation) in the ECR region of the RET gene [5, 8]. Nevertheless, none of these mutations was detected in this pedigree.

Linkage Disequilibrium Analysis

In order to analyze the correlation of variants in the RET gene with the morbidity of MTC/PHEO, we conducted a linkage analysis of the 13 variants in the RET gene and MTC/PHEO using the R package paramlink (table 4). Among the 13 variants, only the heterozygous non-synonymous variant p.D707E in exon 11 showed a significant correlation with MTC (LOD = 3.69) (table 4). Meanwhile, logistic regression analysis indicated that p.D707E may be a risk factor for MTC (OR = 4.413, p = 0.000167). Among the 46 family members of this pedigree, 15 carried the p.D707E variant, 11 had MTC (in-

Fig. 2. Pedigree of the MTC/PHEO patients and their unaffected relatives. Fifteen family members carried the p.D707E variant in the heterozygous form, as indicated by the asterisks. Subjects III-3, III-5, III-18, III-25, IV-3, and IV-15 suffered from MTC alone, and subjects III-2, III-11, III-14, III-19, and IV-2 had MTC accompanied by PHEO; subjects III-15, IV-9, IV-19, and IV-38 were their unaffected relatives.

cluding 6 with MTC alone and 5 with MTC accompanied by PHEO), and the remaining 4 were their unaffected relatives. The distribution of this variant in this pedigree is shown in figure 2, and the nucleotide change in this point mutation is shown in figure 3. However, both the linkage disequilibrium analysis and the logistic regression analysis showed that p.D707E was irrelevant to PHEO (LOD = 0.386, OR = 19.55, $p = 0.995$).

The results of the linkage analysis (HaploView 4.2 software) of all of the SNP in the RET proto-oncogene in the Chinese Han population (from the International HapMap Project) showed that 5 SNP [i.e. p.A432A (rs1800860), p.G691S (rs1799939), p.S904S (rs1800863), c.*15T>C (rs2075912), and c.*731T>C (rs2565200)] detected in this pedigree were linked to each other (fig. 4). Of these, SNP G691S in exon 11 and SNP S904S in exon 15 ($D' = 1.0$, $r^2 = 1.0$, LOD = 12.83), and rs2075912 and rs2565200 ($D' = 1.0$, $r^2 = 1.0$, LOD = 20.23) in the 3'-UTR, were in complete linkage disequilibrium, which is consistent with the results of Sheikholeslami et al. [19].

Table 5. Prevalence of the 11 variants of mutation carriers

Variant	MTC only	MTC+ PHEO	Un-affected	Total	Prevalence, %
p.A45A	8	5	32	45	28.89 (13/45)
p.F285S	0	1	6	7	14.29 (1/7)
C.854_855CA	1	2	6	9	33.33 (3/9)
p.A432A	9	4	32	45	28.89 (13/45)
p.D707E	6	5	4	15	73.33 (11/15)
p.L769L	2	2	19	23	17.39 (4/23)
p.S904S	1	0	12	13	7.69 (1/13)
C.*15T>C	8	5	31	44	29.55 (13/44)
C.*167T>A	5	3	29	37	21.62 (8/37)
C.*731T>C	8	5	30	43	30.23 (13/43)
C.*1506G>A	6	5	28	39	28.21 (11/39)

In an individual in this pedigree, the former 2 SNP (IV-8 in fig. 2, unaffected relative) coexisted, and the latter 2 SNP coexisted in 41 individuals, including all 13 patients.

Fig. 3. Heterozygous aspartic acid-to-glutamate amino acid substitution within exon 11 of the RET gene. Missense c.T2121A (p.D707E) mutation in an MTC patient. The nucleotide change is indicated by the arrows. **a** Wild type. **b** Mutant c.T2121A p.D707E.

Fig. 4. LD plot indicating 5 SNP [i.e. p.A432A (rs1800860), p.G691S (rs1799939), p.S904S (rs1800863), c.*15T>C (rs2075912), and c.*731T>C (rs2565200)] in this pedigree which are linked to each other. The colors from light to dark (white to black) represent the level of linkage disequilibrium (low to high). The numbers in the blocks represent the strength of the association among the SNP, and black blocks indicate complete linkage disequilibrium. SNP in all of the positions are in linkage, and among these rs1799939 and rs1800863, as well as rs2075912 and rs2565200, are in complete linkage disequilibrium ($|D'| = 1$, $r^2 = 1$).

Discussion

HMTC is a rare monogenic autosomal dominant genetic disease, the occurrence and development of which are related to germline mutations of the RET proto-oncogene [20]. Approximately 90% of pedigrees with MEN 2A and familial MTC carry missense mutations in the ECR region cysteine conservative residue (codons 609, 611, 618, and 620 in exon 10 and codons 630 and 634 in exon

11) called hot-spot mutations. These mutations change the protein conformation in the extracellular region, which enhances the transforming capacities of RET, activates tyrosine kinase autophosphorylation, induces cell hyperplasia, and results in various endocrine tumors, including MTC [3, 5]. However, the 13 types of variants of the RET gene that we detected in this pedigree did not have the above hot-spot mutations; of these, p.D707E in exon 11 and p.F285S and c.854_855CA in exon 4 have not

yet been reported, p.D707E in exon 11 might be a risk factor for MTC, and the position of D707 in RET is located in the juxtamembrane region adjacent to the cytoplasmic domain. Bordeaux et al. [21] described RET as a new dependence receptor. It induces apoptosis in the absence of ligand, and the addition of GDNF is then sufficient to block RET proapoptotic activity [21]. The intracellular domain of RET was cleaved by caspase-3, generating 3 main cleavage products (i.e. 42, 40 and 36 kDa) of RET in positions D707 and D1017, inducing apoptosis. Both the D707N and the D1017N point mutations failed to induce cell death. Therefore, we speculate that the mutation D707E detected in this pedigree suppressed RET proapoptosis activity, and caspase-3 could not cleave RET in position D707, resulting in the block of RET-induced cell death. Taken together, this may be involved in the pathogenesis of the endocrine tumors developed in the patients described in our study.

Exons 11 and 13 are important functional regions of the RET gene [3, 10, 22, 23]. Among the 13 variants in this pedigree, except p.D707E, p.G691S in exon 11, and p.L769L and p.V778I in exon 13 are located in the region that also codes ITK. Although statistical analysis showed no correlation between these variants and MTC, the possibility cannot be ruled out.

Since there are no reports of the D707E variant in the RET gene, we could not analyze the correlation between D707E and other SNP in the RET gene in this pedigree via linkage disequilibrium analysis. Eleven individuals carried the D707E variant in this pedigree and had MTC, and hence D707E mutation carriers are at a greater risk for MTC (11/15). There was no correlation between the other variants and MTC in these 11 patients by linkage disequilibrium analysis or logistic regression analysis. Therefore, we speculate that the D707E variant in the RET gene could be solely responsible for the development of MTC. Whether D707E is linked to other SNP in the RET proto-oncogene needs further study.

Kjaer and Ibáñez [24] and Castellone et al. [25] reported that the V292M variant was located in the third cadherin-like domain of the RET gene, and that this structure played a role in the RET gene through its ligand and variants of the structural domain facilitated the activation of the ligand-dependent RET gene. The carcinogenic potential of V292M is weaker than that of C634R and V804M [24, 25]. The newly identified homozygous variants p.F285S and c.854_855CA detected in this pedigree were located in the cadherin-like domain of the RET proto-oncogene, which is closer to V292M. Whether these 2 variants play a role similar to that of V292M needs further study.

Linkage disequilibrium analysis of the correlation of 5 of the 13 SNP in the RET gene showed that SNP G691S in exon 11 (rs1799939) and SNP S904S in exon 15 (rs1800863) were in complete linkage disequilibrium, which is consistent with a previous report [23]. SNP G691S and S904S are associated with the development of MTC in patients who carry germline mutations of the RET gene [26–29]. They appear to influence the onset of HMTc, and the age at diagnosis of MTC in these homozygous pleomorphic patients is 10 years earlier than that for heterozygous MEN 2A or patients with the wild-type haplotype [30, 31]. However, linkage analysis in this pedigree showed no linkage of SNP G691S and S904S with MTC, which is contrary to the above reports. This may be due to the coexistence of SNP G691S and SNP S904S in only one individual in this pedigree (IV-8 in fig. 2), i.e. a 29-year-old female without MTC at the time of reporting. As a consequence, we are unable to confirm whether individuals in whom SNP G691S and SNP S904S coexist in this pedigree would influence the onset of HMTc.

Whether the highly linked rs2075912 and rs2565200 in the 3'-UTR of the RET gene are associated with MTC needs further study.

The 13 variants of the RET gene in this pedigree are different from the hot-spot mutations that were reported in other pedigrees, especially the vital variant D707E. Screening of these 13 variants in this pedigree may provide the basis for the prevention of HMTc and play an instructive role in the clinical management of patients with MTC.

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Author Contributions

Lu Zhang, Xiaoyu Li, Shengxiang Ge, Fengjie Qi, and Yongxing Zhang contributed pertinent aspects of the planning. Mengyuan Chen, Shuizhen Huang, Shupeng Zhao, and Binbin Chen contributed pertinent aspects of the conduct. Peng Li, Bogang Teng, Jing Xu, Qiyuan Li, and Yongxing Zhang contributed pertinent aspects of the report.

Disclosure Statement

Lu Zhang, Xiaoyu Li, Shengxiang Ge, Fengjie QI, Mengyuan Chen, Shuizhen Huang, Shupeng Zhao, Binbin Chen, Peng Li, Bogang Teng, Jing Xu, Qiyuan Li, and Yongxing Zhang declare that they have no conflicts of interest.

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Erratum

In the article by Zhang et al., entitled “Rare RET Variant p.D707E in a Chinese Pedigree with Hereditary Medullary Thyroid Carcinoma” [Pathobiology DOI: 10.1159/000448845], the author “Dai Wang” with the affiliation “a” was missing in the original publication. The correct authorship is as follows:

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Moreover the acknowledgement was incomplete and must be as follows:

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