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ORIGINAL ARTICLE

RET mutation Tyr791Phe: the genetic cause of different diseases derived from neural crest

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Abstract Activating germline *RET* mutations are presented in patients with familial medullary thyroid carcinoma (FMTC) and multiple endocrine neoplasia (MEN) types 2A and 2B, whereas inactivating germline mutations in patients with Hirschsprung's disease (HSCR). The aim of this study was to evaluate genotype–phenotype correlations of the frequently discussed Tyr791Phe mutation in exon 13 of the *RET* proto-oncogene. Screening of three groups of patients was performed (276 families with medullary thyroid carcinoma (MTC), 122 families with HSCR, and 29 patients with pheochromocytoma). We found this mutation in 3 families with apparently sporadic MTC, 3 families with FMTC/MEN2, 1 patient with pheochromocytoma, and 3 families with HSCR. All gene mutation carriers have a silent polymorphism Leu769Leu in exon 13. In three families second germline mutations were detected: Cys620Phe (exon 10) in MEN2A family, Met918Thr (exon 16) in MEN2B family, and Ser649Leu (exon 11) in HSCR patient. Detection of the Tyr791Phe mutation in MEN2/MTC and also in HSCR families leads to the question whether this mutation has a dual character (gain-of-function as well as loss-of-function). A rare case of malignant pheochromocytoma in a patient with the Tyr791Phe mutation is presented. This study shows various clinical characteristics of the frequently discussed Tyr791Phe mutation.

Keywords *RET* proto-oncogene · *RET* mutation · Medullary thyroid carcinoma · Hirschsprung's disease · Pheochromocytoma · Genetics

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Introduction

Neurocristopathies can be divided according to Bolande classification into simple and complex neurocristopathies. In the group of simple neurocristopathies there are dysgenetic diseases including Hirschsprung's disease (HSCR) and neoplastic diseases including pheochromocytoma and medullary thyroid carcinoma (MTC). Complex neurocristopathies cover multiple endocrine neoplasia type 2A and 2B syndromes (MEN2A, MEN2B) [1]. All mentioned neurocristopathies are linked with the *RET* proto-oncogene as the major genetic cause of their development. The *RET* proto-oncogene is expressed in neural crest-derived cells, including enteric and sympathetic neurons, adrenal chromaffin cells, and parafollicular C-cells of the thyroid gland.

The *RET* proto-oncogene is located on 10q11.2; it is composed of 21 exons and encodes a transmembrane tyrosinekinase receptor [2].

MTC and pheochromocytoma are tumors derived from parafollicular C-cells of the thyroid and chromaffin cells of the adrenal medulla, respectively. Twenty-five percent of MTC represent autosomal dominant inherited disease with variable penetration in families and variable organ manifestation—FMTC, MEN2A, and MEN2B. FMTC is characterized by the familial occurrence of MTC without other lesions. MEN2A is characterized by MTC, pheochromocytoma (50% of cases), and/or hyperparathyroidism (20% of cases). The most aggressive variant of MTC appears in conjunction with marfanoid habitus, ganglioneuromatosis, bumpy lips, diarrhea, mucosal neuromas, and pheochromocytoma (50% of cases) in MEN2B syndrome [3]. The genetic causes of MTC and partly of pheochromocytoma are germline or somatic activating mutations in the *RET* proto-oncogene. The risk exons for MTC are 5, 8, 10, 11, 13, 14, 15, and 16. The activating mutations typical for MEN2A are located in exons 10 and 11, for MEN2B and pheochromocytoma in exons 15 and 16, and for FMTC they are spread within exons 5, 8, 10, 11, 13, 14, and 15 [4].

On the other hand, HSCR is characterized by congenital aganglionosis of the submucosal and myenteric neural plexuses of the colon. Three forms are distinguished—short form or long form of HSCR and total colonic aganglionosis. Sporadic cases are represented by 85% and familial cases by 15% of HSCR patients. HSCR is suggested as an oligogenic disease, whereas the major causing gene is the *RET* proto-oncogene and its inactivating germline missense mutations, insertions, or deletions. The inactivating mutations are found in almost all exons in HSCR patients. In 5% of HSCR there is a genetic overlap with MTC and there is a high risk of MTC or MEN2 development. In these patients dual "Janus" mutations in exon 10 were observed [5–7].

Here we focused on the prevalence and clinical manifestation of the Tyr791Phe mutation in exon 13 in our cohorts of MTC, HSCR, and apparently sporadic pheochromocytoma. This mutation was firstly published as a de novo mutation in one patient with HSCR [8] and 1 year later as a new hot spot for MTC [9]. Recently, functional studies about the Tyr791Phe mutation were published. Tyr791Phe RET receptor mutant is a monomeric receptor that is autophosphorylated and activated independently on typical RET ligand–glial cell-line derived neurotrophic factor (GDNF). This mutation results in a modification of the tertiary structure of the catalytic domain and leads to a protein with more accessible substrate and ATP-binding conformation. A high degree of RET mutant is expressed at the plasma membrane [10]. The Tyr791Phe mutation increased proliferative properties, colony formation, tumor growth, and apoptotic resistance in in vitro studies [11]. Tyr791Phe RET mutant also plays an important role in cell mitogenicity and transformation [12]. To the best of our knowledge, no functional studies have been performed in connection with HSCR pathogenesis.

Results

The direct sequencing analysis of the *RET* proto-oncogene revealed a germline mutation Tyr791Phe in exon 13 in 10 index patients and 21 of their family members—gene carriers. Families with detected germline Tyr791Phe mutation are described in detail in Table 1. All patients and gene Tyr791Phe mutation carriers also have a silent polymorphism Leu769Leu (CTT/CTG) in exon 13.

Three families (A, B, and H) were recently published by us [13, 14]. The index patient from family G underwent adrenalectomy at the age of 38 for a large pheochromocytoma producing only norepinephrine with histologically proven metastases to adjacent lymph nodes. Before that, he had been followed for hypertension for 15 years. During the subsequent follow-up, two reoperations due to local recurrence of the tumor were performed. Prophylactic total thyroidectomy was performed after detecting a germline Tyr791Phe mutation. The index patient from family I has been treated for HSCR since his birth. He has just completed treatment for acute lymphoblastic leukemia (ALL).

In three families (A, B, and J) double germline mutations were detected. Beside the Tyr791Phe mutation, Met918Thr (exon 16) in family A, Cys620Phe (exon 10) in family B, and Ser649Leu (exon 11) in family J were detected. All of these additional mutations were described previously as causing mutations for MTC and in the first and second cases these mutations seem to determine the phenotype.

Detection rates as well as clinical characteristics of Tyr791Phe mutation carriers are summarized in Table 2.

Discussion

We present here 31 carriers of the Tyr791Phe mutation from 10 families. A high clinical variability was associated with this mutation: 8 MTC, 11 C-cell hyperplasia (CCH), 2 micro papillary thyroid carcinomas (PTC), 4 HSCR, 1 malignant pheochromocytoma, and 11 as yet unoperated clinically asymptomatic carriers. Before molecular genetic analysis, three families were clinically classified as sporadic MTC where the germline mutations were observed as a de novo mutation/low penetrance in index patients (Tyr791Phe present in 27.3% of sporadic MTC cases with detected germ-line *RET* mutation). Our screening revealed the Tyr791Phe mutation in one FMTC family. We also

Table 1 Clinical manifestation of the Tyr791Phe mutation in index patients and family gene carriers of the mutation

Family	Clinical group	Probands	Sex	Age (years)	Preoperative' CT	Age of TTE (years)	TTE histology (TNM)	Follow-up	Pheochromocytoma	HSCR form	Additional mutation
A[a]	MEN2B	Index patient	F	†	Increased	14	MTC (T2NxMx)	Died (33 years)	Both side (31 years)		Met918Thr
		Son	M	17	Increased	7	MTC (T1N1M0)	Recurrence	Suspected		
		Son	M	12	Increased	5	MTC (T1N1M0)	Normal CT			
B[a]	MEN2A	Index patient	M	63	Increased	58	MTC (T1N1M0)	Normal CT			Cys620Phe
		Daughter	F	43	Normal	40	CCH	Normal CT	Left (30 years)		
		Daughter	F	34	Normal	31	CCH	Normal CT			
		Granddaughter	F	22	Normal	19	CCH	Normal CT			
		Granddaughter	F	20	Increased	17	CCH	Normal CT			
		Granddaughter	F	11	Normal	8	CCH	Normal CT			
C	FMTC	Index patient	F	68	–	–	TTE refused	Normal CT			
		Sister[b]	F	†	–	?	MTC	Died (60 years)			
		Sister[b]	F	†	–	?	MTC	Died (?)			
		Son	M	44	Normal	43	CCH	Normal CT			
		Grandson	M	11	Normal	9	CCH	Normal CT			
D	Spor MTC	Index patient	F	84	Increased	69	MTC (T4N1M0)	Normal CT			
		Son	M	55	–	–	TTE recommended	Normal CT			
E	Spor MTC	Index patient	F	55	Increased	55	MTC (T4N1M0) + microPTC	Increased CT			
		Mother	F	75	–	–	TTE refused	Normal CT			
		Son	M	33	Normal	33	Normal	Normal CT			
		Son	M	30	Normal	30	CCH	Normal CT			
		Grandson	M	6	Normal	6	CCH	Normal CT			
F	Spor MTC	Index patient	F	22	Normal	19	MicroPTC + CCH	Normal CT			
		Father	M	53	–	–	TTE recommended	Normal CT			
		Sister	F	23	–	–	TTE recommended	Normal CT			
		Brother	M	18	–	–	TTE recommended	Normal CT			
G	Pheochromocytoma	Index patient	M	46	Normal	44	CCH	Normal CT	Right (38 years), malignant		
		Mother	F	68	–	–	TTE refused	?			
H	HSCR	Index patient	F	27	–	–	TTE refused	No cooperation		Pseudo[c]	
I	HSCR	Index patient[d]	M	17	–	–	TTE recommended	Normal CT		TCA	
		Sister	F	9	–	–	TTE recommended	Normal CT		Classical	
J	HSCR	Index patient	M	20	–	–	TTE recommended	?		TCA	Ser649Leu

TCA total colonic aganglionosis, *TTE* total thyroidectomy, *CT* calcitonin

[a] Recently published in [13]

[b] Lived abroad

[c] Pseudo HSCR—histologically present nonfunctional neural ganglia

[d] After treatment for acute lymphoblastic leukemia

?: not known

†: died

Table 2 Detection rate of the Tyr791Phe mutation in different cohorts

	MTC ($n = 276$)				Pheochromocytoma	HSCR
	Sporadic MTC	FMTC	MEN2A	MEN2B		
Total number of families	245	10	14	7	29	122
Families with activating *RET* mutation	11	5	13	7	3	8
Families with the Tyr791Phe mutation	3	1	1	1	1	3
Tyr791Phe detection rate (%)	1.2	10	7.1	14.3	3.5	2.5
Tyr791Phe (%) of detected mutations	27.3	20	7.7	14.3	33.3	37.5

found the Tyr791Phe mutation in one MEN2A and one MEN2B family where it was accompanying apparently more aggressive *RET* mutations (as discussed below). Interestingly, total Tyr791Phe detection rates are nearly similar in our pheochromocytoma and HSCR cohorts (33.3 and 37.5%, respectively). We did not find other additional associated endocrinopathies that had been published previously—such as coexistence of MEN1 syndrome [15], hyperparathyroidism or hyperprolactinemia [16–18], and acromegaly [19].

The Tyr791Phe mutation was only observed in a few cases of pheochromocytomas [9, 18, 20–22]. In our study, three patients (9.7%) with the Tyr791Phe mutation had pheochromocytoma—two of them (families B with MEN 2A and G) as the first clinical manifestation, the third one (family A) in association with MEN2B phenotype. It is probable that the Cys620Phe mutation was the real cause of pheochromocytoma in this patient with MEN2A rather than Tyr791Phe. The index patient from family G had histologically confirmed CCH. Usually, the risk of malignancy in pheochromocytoma is very low [21, 23]. The occurrence of malignant pheochromocytoma in the patient from family G among subjects with MEN2 is very unusual and to the best of our knowledge, this is the first described patient with this mutation. Testing for other candidate genes such as succinate dehydrogenase subunits B and D and VHL were negative, however, we cannot exclude other mutations in some other candidate genes. Our study supports that the Tyr791Phe mutation may contribute to the causes of familial pheochromocytoma [22].

In two patients with the Tyr791Phe mutation we found the co-occurrence of microPTC with MTC or CCH (family E and F). It was only found in a small number of families with Tyr791Phe in the entire world [24–26]. But it remains as an open question whether the simultaneous occurrence of inherited MTC and PTC is coincidental or the result of a partly common pathogenic pathway. It was suggested that there could be a possible correlation between the occurrences of PTC and *RET* mutation in exon 13 that affects the intracellular domain of the encoded protein [25].

Surprisingly, we have detected the Tyr791Phe mutation in three HSCR families (family H, I, and J, i.e., in 37.5% of HSCR families with *RET* mutations detected in MTC risk exons) that do not correspond to some special form of HSCR. Mostly, typical HSCR mutations are inactivating and are found along the whole gene. Originally, the Tyr791Phe mutation was observed as de novo in one HSCR patient without MTC [8]. Detection of the Tyr791Phe mutation in HSCR families leads to the question whether this mutation has a dual "Janus" character (gain-of-function as well as loss-of-function) such as mutations described only in exon 10 (codons 609, 611, 618, and 620) in all HSCR/MEN2A patients [5–7]. These dual "Janus" mutations are dependent on target tissue: in the thyroid they lead to uncontrolled proliferation of C-cells and in the colon to apoptosis of enteric neural ganglia. We strongly recommend screening exon 13 along with exon 10 in all HSCR patients to avoid the risk of MTC.

A further interesting finding of our study was the detection of double germline mutation in three families (family A, B, and J). Overview information about the families with multiple germline mutations in the world is collected in our previous publication [13]. The detection of activating mutation Ser649Leu in HSCR patient (family J) is the first report about it. This mutation was reported previously in apparently sporadic MTCs [17, 27, 28] with low penetrance of MTC and relatively low aggressive potential of the disease.

Polymorphism Leu769Leu was detected in all carriers with Tyr791Phe and it is probably in linkage disequilibrium with this mutation. The association of the mutation with this polymorphism suggests that the polymorphisms could have a potential role as a genetic modifier [29, 30]. Additional genetic alterations either in other exons of the *RET* proto-oncogene or in other genes could explain the phenotypic variability associated with the Tyr791Phe mutation, modify disease susceptibility, or clinical phenotype [30].

Tyr791Phe was described as a minor mutation in FMTC/MEN2A families with phenotypic heterogeneity and variability of age at diagnosis. The late onset of MTC as well as no deaths of gene carriers, gene carriers with finding of normal histology and high cure rates have been documented [9, 18, 19, 24, 31]. The behavior of the Tyr791Phe mutation was rather aggressive in our families

as demonstrated by two patients who had T4N1M0 tumors with infiltrative and aggressive growth of tumor at the age of 55 and 69 years, respectively. It is a pity that clinical data of two family members of FMTC family who probably died due to MTC are not available. In our patients there was a very large difference in age at diagnosis of MTC in the index cases—from 14 to 69 with different TNM classification. CCH was revealed in very early age—in 6- and 9-year-old carriers. On the other hand, the oldest asymptomatic carrier of the mutation in our cohort was 75-years-old. Eight patients were operated on with MTC and 11 with CCH histological results. Eleven gene carriers were not yet operated on and they are clinically without any MTC symptoms. Despite the fact that the mutation was categorized as the least-high risk mutation [18, 31–33], we tend to agree with recommendation to perform prophylactic total thyroidectomy in all carriers of the mutation regardless of calcitonin levels, ideally before 10 years of age [19, 32, 33]. Thanks to high variability of families with the Tyr791Phe mutation, and in some patient's early onset of disease, it is impossible to exclude or predict the age of MTC development [34–36]. Recently the Tyr791Phe mutation was presented as the cause of the occurrence of MTC in 15- and 19-year-old patients, which is the youngest age reported in literature [35]. On the other hand, by that time some studies preferred postponing TTE to the age of 20 years [37] or to the third decade of life [31] or preferred only screening calcitonin levels [38] because of few cases with local lymph node metastases, low tendency to metastasize and no deaths described with the Tyr791Phe mutation. But our cohorts refute these classical statements about mild behavior of tumor with the Tyr791Phe mutation. Thus, optimal timing for surgery in patients carrying *RET* Tyr791Phe mutation remains controversial. We hope that our cohort of patients contributes to the worldwide series of patients with this mutation.

Materials and methods

Cohorts

Molecular genetic analysis was performed in 276 families with MTC (including 14 MEN2A, 7 MEN2B, 10 FMTC families, and 245 apparently sporadic MTC cases), 29 patients with apparently sporadic pheochromocytoma and 122 families with HSCR. Database of pedigrees was created with the Cyrillic 3 program. The basal and pentagastrin or calcium stimulated calcitonin levels were measured with RIA kit (DSL-1200, Webster, TX, USA). Basal and stimulated calcitonin values below 40 and 200 pg/ml, respectively, were considered normal. Tumor staging was performed according to the International union against cancer tumor-node-metastasis (TNM) classification from 2002. CCH was defined as 50 C-cells per low-power field.

Genetic analysis

Signed informed consent for this study was obtained from each patient and family member who participated. Genomic DNA was extracted from peripheral leucocytes using QIAamp blood kit (Qiagen, Hilden, Germany). PCR amplification of DNA samples of exons 10, 11, 13, 14, 15, and 16 and the subsequent double-stranded fluorescent sequencing were performed according to our previously described procedure [39] on ALFExpress Automated DNA Sequencer (Pharmacia, Sweden) or on CEQ 8000 Sequencer (Beckman Coulter, USA). For the sequenase reaction the previously purified PCR products (Agencourt Ampure kit, Beckman Coulter, USA), the same unlabeled primers (as previously described) and the Quick Start kit (Beckman Coulter, USA) were used. Then, PCR products were re-purified (Agencourt CleanSEQ kit, Beckman Coulter, USA), sequenced and analyzed by CEQ 8000 sequencing software.

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