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A novel Czech kindred with familial medullary thyroid carcinoma and Hirschsprung's disease

Šárka Dvořáková[a,*], Kateřina Dvořáková[b], Marcela Malíková[c], Richard Škába[d], Petr Vlček[e], Běla Bendlová[a]

[a]*Department of Molecular Endocrinology, Institute of Endocrinology, Prague 11694, Czech Republic*
[b]*Department of Clinical Endocrinology, Institute of Endocrinology, Prague 11694, Czech Republic*
[c]*Institute of Biology and Medical Genetics, 2nd Faculty of Medicine, Charles University and Hospital Motol, Prague 15006, Czech Republic*
[d]*Clinic of Paediatric Surgery, 2nd Faculty of Medicine, Charles University and Hospital Motol, Prague, 15006, Czech Republic*
[e]*Department of Nuclear Medicine, 2nd Faculty of Medicine, Charles University and Hospital Motol, Prague, 15006, Czech Republic*

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Abstract

Purpose: The *RET* proto-oncogene is involved in neural crest disorders. Activating germline mutations in the *RET* proto-oncogene cause the development of familial medullary thyroid carcinoma (FMTC) or medullary thyroid carcinoma (MTC) as a part of multiple endocrine neoplasia type 2 (MEN2) syndrome. Inactivating germline mutations in the *RET* proto-oncogene are detected in Hirschsprung's disease (HSCR). Only in a very small number of families are these 2 diseases expressed together.

Methods: This study presents a novel Czech kindred with FMTC-HSCR phenotype. Two family members (mother and daughter) were tested for *RET* germline mutations in exons 10, 11, 13, 14, 15, and 16.

Results: Direct fluorescent sequencing of genomic DNA revealed a heterozygous mutation in the *RET* proto-oncogene in exon 10 at codon C609Y in both persons tested. This family was reclassified, thanks to genetic screening from the apparently sporadic MTC-HSCR to FMTC-HSCR.

Conclusion: The germline mutation was detected because of the systematic genetic screening of the *RET* proto-oncogene, which is useful for genetic counseling of potential risk of HSCR and MTC in other family members. This family could be added to the small worldwide cohort of families with MEN2A/FMTC-HSCR.

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The human *RET* proto-oncogene, which is located on chromosome 10q11.2 and consists of 21 exons, encodes a transmembrane tyrosine kinase receptor. It plays a critical role in embryonic enteric nerve development, differentiation, migration, and neoplastic growth of cells derived from neural crest lineage [1]. *RET* gene is also involved in the

* Corresponding author. Department of Molecular Endocrinology, Institute of Endocrinology, Narodni 8, Prague 1, 116 94 Czech Republic. Tel.: +42 022 490 5301; fax: +42 022 490 5325.
E-mail address: sarka@obloha.cz (S. Dvořáková).

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development of the mammalian kidney [2]. The function of the RET protein is based on the extracellular binding of ligands and coreceptors, dimerization of receptor through cysteine-rich domain, and intracellular autophosphorylation of tyrosine kinase catalytic domain. Changes in the sequence of *RET* gene are associated with inherited neurocristopathies—mainly MEN2 syndromes and HSCR [1].

Germline mutations in the *RET* proto-oncogene are well documented as a genetic cause of autosomal dominant inheritance of medullary thyroid carcinoma (MTC). Three clinically distinct hereditary forms are known: familial medullary thyroid carcinoma (FMTC), multiple endocrine neoplasia type 2 A (MEN2A), and multiple endocrine neoplasia type 2 B (MEN2B). Familial medullary thyroid carcinoma is characterized by the familial occurrence of MTC without other lesions. MEN2A is characterized by MTC, pheochromocytoma, and/or hyperparathyroidism. The most aggressive variant of MTC appears in conjunction with marfanoid habitus, ganglioneuromatosis, bumpy lips, diarrhea, mucosal neuromas, and pheochromocytoma in MEN2B syndrome associated with a very early onset of MTC. Most patients with MEN2A harbor a missense mutation at 1 of 5 cysteine residues within the extracellular domain of *RET* (exons 10 and 11), and in patients with FMTC, missense mutations have been additionally identified in a region of the *RET* gene encoding the intracellular tyrosine kinase domain (exons 13, 14, and 15). The MEN2B phenotype is in more than 98% of patients caused by a single mutation (M918T, exon 16), which affects the catalytic core pocket of the receptor [3,4].

Hirschsprung's (HSCR) disease is characterized by the absence of intramural ganglion cells in the submucosal and myenteric plexus along a variable length of the distal gastrointestinal tract, often resulting in intestinal obstruction in neonates. This lack of ganglia is thought to be the result of a premature arrest in the migration and/or differentiation of enteric neuroblasts, which highly express RET protein during embryogenesis. The *RET* germline inactivating mutations are detected in up to 49% of familial HSCR (mainly the long segment form of HSCR) and in up to 35% of sporadic HSCR. The changes contain deletions, frame shifts, nonsense, or missense mutations scattered along the whole *RET* proto-oncogene. Hirschsprung's disease is inherited most probably as an oligogenic disease [5-8].

Co-segregation of MEN2A/FMTC with HSCR phenotype is infrequently reported [9-21]. To the best of our knowledge, there were no more than 30 families described in the world so far. These families are linked to the *RET* exon 10 mutations at codons 609, 611, 618, and 620. Some families are described as having FMTC-HSCR; others as having MEN2A-HSCR without association with the specific type of mutation. Moreover, a variable length of HSCR forms was detected independently of the type of mutations in these families. We report here a novel Czech kindred with FMTC-HSCR phenotype determined by C609Y mutation.

1. Materials and methods

1.1. Patients

Fig. 1 presents the pedigree of the kindred. Two family members tested signed informed consent in accordance with institutional ethical guidelines and national rules. The proband's family history was negative for HSCR and for bowel diseases in general as well as for MEN2 tumors and cancer in general. Relatives of the patient apart from the mother could not be approached for DNA analysis.

The proband is a 26-year-old woman with both HSCR and MTC in her medical history. The diagnosis of the long segment form of HSCR was made by gastrointestinal tract contrast study and by biopsy 3 weeks after her birth, and an ileostomy was performed. The aganglionic portion of the bowel consisted of whole colon and 15 cm of terminal ileum. She underwent Martin's original ileoleft colon anastomosis with Kasai ileorectoplasty without protective enterostomy at 3 years of age [22]. Hirschsprung's disease was confirmed by histological investigation of the resected bowel using histochemical staining for α-naphthylesterase and acetylcholinesterase. At present, she has regular defecation twice or 3 times per day, good discrimination of stool quality, and no sexual dysfunction.

At the age of 21 years, the proband underwent total thyroidectomy for medullary thyroid carcinoma followed by external radiotherapy to the neck area. Then an interval without any sign of recurrence of the disease followed; basal and stimulated levels of calcitonin were in normal range. Four years after the surgery, the patient reported a 6-month history of lump growth in the right pole of the scar after thyroidectomy. Basal and stimulated calcitonin levels increased, and cytology after fine-needle aspiration biopsy from this lump revealed relapse of poorly differentiated thyroid cancer. Computed tomography of the neck and upper mediastimum demonstrated an 8 × 4−mm lump in the right lower pole of the supposed thyroid gland. Metaiodobenzylguanidine I 123 scintigraphy showed no

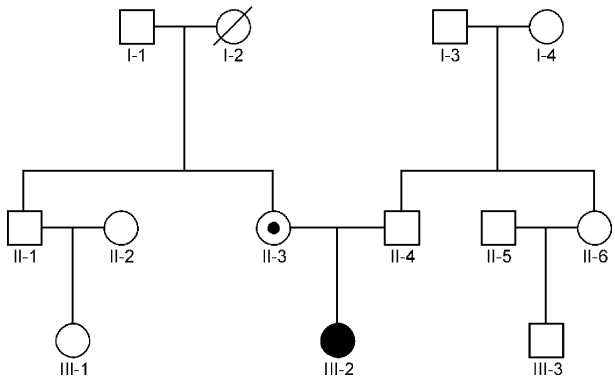

Fig. 1 The pedigree of the described family. The index patient is III-2 with FMTC and HSCR. The II-3 family member is an asymptomatic carrier of mutation.

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