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## Case Report

## KIT Mutation in Gastric Gastrointestinal Stromal Tumor in a Patient With Familial Paraganglioma Syndrome Type 4

Robyn L. Houlden, MD<sup>\*</sup>, Cassandra L.A. Hawco, MD

Department of Medicine, Queen's University, Kingston, Ontario, Canada

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## ABSTRACT

**Objective:** Familial paraganglioma syndrome type 4 is associated with mutations in the succinate dehydrogenase complex subunit B (SDHB) gene. We report the case of a patient with familial paraganglioma syndrome type 4 with the mutation c.600G>T; p.Trp200Cys who developed a gastric gastrointestinal stromal tumor (GIST) with a KIT mutation.

**Methods:** Clinical, radiographic, and genetic data have been presented.

**Results:** A 40-year-old man with familial paraganglioma syndrome type 4 and recurrent paraganglioma presented with epigastric pain. He had undergone resection of a paraganglioma superior to the right adrenal gland at 19 years of age, resection of two para-aortic paragangliomas at 39 years, and resection of a paraganglioma in the interatrial septum at 40 years. Computed tomography scan showed a 3.2 × 3.8-cm gastric body intraluminal polypoid mass. A partial gastrectomy was performed, which revealed a GIST with a KIT mutation (NM\_000222.2[KIT]:c.2466T>A[p.Asn822Lys]).

**Conclusion:** This case provides further evidence that mutations in SDHB and KIT are not mutually exclusive with GISTs. It also identifies the need for endoscopic evaluation for GIST in patients with familial paraganglioma syndrome type 4 with unexplained gastrointestinal symptoms.

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## Introduction

GISTs are neoplasms that arise from mesenchymal gastrointestinal tissues.<sup>1</sup> They occur anywhere along the gastrointestinal tract and are found most commonly in the stomach (50%–60%) and small intestine (30%–35%) and less frequently in the colon, rectum, and esophagus.<sup>1</sup> The vast majority of GISTs are sporadic and occur in older adults.<sup>2</sup> In approximately 5% of cases, there is an association with a genetic or idiopathic multi-tumor syndrome, including type 1 neurofibromatosis, familial GIST syndrome, Carney-Stratakis syndrome, and Carney triad.<sup>3</sup>

GIST tumors can be subclassified into succinate dehydrogenase (SDH)-competent and SDH-deficient groups.<sup>2</sup> The SDH enzyme complex is located in the inner mitochondrial membrane and connects the oxidation of succinate to fumarate in the Krebs cycle to the reduction of coenzyme Q in the mitochondrial electron

transport chain.<sup>4</sup> It is composed of four subunits (SDH A to D). Genetic or epigenetic alterations in any of the four genes encoding for these subunits can lead to the destabilization of the SDH complex, resulting in the accumulation of succinate and the activation of cellular pathways leading to increased angiogenesis and cellular proliferation.<sup>4</sup>

Up to 85% of GISTs are SDH-competent with mutually exclusive mutations in KIT or platelet-derived growth factor A (PDGFRA).<sup>5,6</sup> KIT and PDGFRA proteins are growth factor receptors activated by ligands such as PDGF-AA and stem cell factor, triggering cellular pathways that upregulate proliferation and downregulate apoptosis. Mutations of KIT and PDGFRA cause the activation of cellular pathways, which leads to spontaneous proliferation and uncontrolled tumor growth. Other SDH-competent GISTs include tumors with NF1, BRAF mutations, or other rare mutations in ARID1A, ARID1B, CBL, FGFR1, NRAS, HRAS, KRAS, MAX, MEN1, and PIK3CA as well as novel gene fusions (KIT-PDGFRA and ETV6-NTRK3).<sup>2</sup>

The SDH-deficient GIST group includes the majority of pediatric GISTs, some sporadic adult cases, and GIST syndromes including the Carney triad and Carney-Stratakis-Syndrome.<sup>2</sup> The Carney triad consists of gastric GIST, paraganglioma, and pulmonary chondroma and is seen mainly in girls and young women.<sup>7</sup> GISTs associated with the Carney triad show the loss of expression of SDHB by immunohistochemistry caused by epigenetic silencing of the SDHC

**Abbreviations:** CT, computed tomography; GIST, gastrointestinal stromal tumor; MIBG, meta-iodobenzylguanidine; MRI, magnetic resonance imaging; PDGFRA, platelet-derived growth factor A; SDHB, succinate dehydrogenase complex subunit B.

<sup>\*</sup> Address correspondence and reprint requests to Dr. Robyn Houlden, Division of Endocrinology, Kingston General Hospital, 76 Stuart Street, Kingston, ON, K7L 2V7, Canada.

E-mail address: [houlden@queensu.ca](mailto:houlden@queensu.ca) (R.L. Houlden).

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gene through promoter hypermethylation.<sup>8</sup> Carney-Stratakis syndrome consists of hereditary GIST and paraganglioma and is associated with germline mutations in SDHB, SDHC, and SDHD.<sup>9</sup>

Historically, it has been believed that SDH-deficient GISTs are mutually exclusive to KTI/PDGFR $\alpha$ /BRAF/NF1/KRAS mutations.<sup>10</sup> We report the case of a patient with familial paraganglioma syndrome type 4 (SDHB mutation c.600G>T; p.Trp200Cys) who developed a gastric GIST that possessed a KIT mutation (NM\_000222.2 [KIT]:c.2466T>A[p.Asn822Lys]). This case provides evidence that mutations in SDHB and KIT are not mutually exclusive with GISTs.

## Case Report

A 57-year-old man presented with recurrent epigastric pain. He had been previously diagnosed with familial paraganglioma syndrome type 4. At 19 years of age, he had developed headaches, hypertension, and episodic lightheadedness. Twenty-four hour catecholamine excretion was increased, and a computed tomography (CT) scan revealed a tumor arising from the right adrenal gland, which was subsequently excised. Pathology was compatible with an extra-adrenal paraganglioma.

At 39 years of age, the patient developed episodes of headache and palpitations. Twenty-four hour urine collections revealed elevated catecholamine excretion. 131-I-labeled meta-iodobenzylguanidine (MIBG) scanning revealed two paragangliomas: a 3-cm lesion in the mid abdomen and a 2-cm lesion 6 cm inferior. Both lesions as well as the right adrenal gland were surgically resected. Pathology was compatible with recurrent paragangliomas and not nodal metastases as no lymphoid tissue was seen. The right adrenal gland had normal histology.

Postoperatively, urinary catecholamine excretion remained elevated. Repeat 131-I MIBG scanning revealed uptake near the mediastinum. CT and MRI scans revealed a 5.5 × 3.0 × 4.5 cm mass in the interatrial septum causing compression and displacement of the superior vena cava, right pulmonary vein, and left atrium. Surgery was performed with excision of a 5.5 × 4.0 × 3.5 cm paraganglioma involving both atria. Most of the atrial tissue was excised and required patch reconstruction and dual chamber pacemaker insertion. Pathology was compatible with a recurrent paraganglioma.

Genetic testing at the University of Pittsburgh Medical Center revealed a previously unpublished mutation (c.600G>T; p.Trp200Cys),<sup>11</sup> which was felt to be a variant of uncertain significance. The laboratory reported they had seen the variant in two other families, one of which had features of hereditary paraganglioma. Our patient's family history showed that his mother had died at 39 years of age of metastases from a carotid body tumor.<sup>12</sup> Her autopsy revealed metastases in the liver and intestinal tract compatible with malignant paraganglioma.

After his most recent surgery, the patient had been followed up annually with clinical assessment, 24-hour urinary metanephrine collection, and CT scanning of the neck/chest/abdomen with no evidence of recurrent paraganglioma. He presented with a several-month history of recurrent epigastric discomfort. A CT scan revealed a 3.2 × 3.8 cm gastric body intraluminal polypoid mass that had not been visualized on a CT scan one year earlier. A laparoscopic partial gastrectomy was performed with resection of a 3.8 × 3.1 × 3.0 cm tumor. Pathology revealed a mixed GIST. Histologic grade was G2 (high grade; mitotic rate > 5/5 mm<sup>2</sup>). Surgical margins were uninvolved. Immunohistochemical studies were positive for KIT (CD117) and DOG1 (ANO1). SDHB staining was not available. A massively parallel sequencing assay (OncoPrint Comprehensive V3, ThermoFisher) confirmed a KIT mutation (NM\_000222.2[KIT]:c.2466T>A[p.Asn822Lys]). This variant results in activation of KIT kinase (PMID 24205792, 31484543) and has been associated with resistance to imatinib (PMID 18488168).

The patient's other past medical history included phenylketonuria with moderate intellectual challenge (noncompliance with low phenylalanine diet), gastrointestinal reflux disease, chronic back pain, depression, obstructive sleep apnea, restless legs syndrome, and benign prostatic hypertrophy. Medications consisted of pantoprazole 20 mg twice daily, domperidone 20 mg twice daily, digoxin 0.25 mg daily, bisoprolol 10 mg twice daily, furosemide 20 mg daily, atorvastatin 40 mg daily, apixaban 5 mg daily, tamsulosin 0.4 mg daily, mirabegron 50 mg daily, olanzapine 5 mg daily, sertraline 100 mg daily, galantamine 8 mg twice daily, and gabapentin 100 mg three times daily.

## Discussion

Recent evidence has challenged the belief that SDH mutations are mutually exclusive from KIT or PDGFR $\alpha$  mutations. Our case and several other published reports have illustrated patients with known somatic mutations in the SDH gene who developed a GIST associated with a KIT or PDGFR $\alpha$  mutation.<sup>13–18</sup> To the best of our knowledge, this is the second case of a patient with a somatic SDHB gene mutation and a KIT mutation-positive GIST. Jové et al<sup>15</sup> described the case of a 29-year-old man with a gastric GIST containing an activating KIT mutation who was diagnosed with familial paraganglioma syndrome type 4 at 13 years of age following the removal of a paraganglioma. Brcic et al<sup>2</sup> described a 50-year-old patient who had a gastric GIST with a point mutation in exon 5 of the SDHA gene and a mutation in exon 11 of the KIT gene. The authors hypothesized that the SDHA mutation was the most likely driver and that the KIT mutation was a secondary event reflecting clonal evolution.

Patients with hereditary paraganglioma-pheochromocytoma syndromes should have annual biochemical and clinical surveillance for signs and symptoms of paraganglioma-pheochromocytoma as well as biennial full-body MRI examinations starting between the ages of 6 and 8.<sup>19</sup> Endoscopic evaluation for GISTs should be performed in individuals with unexplained gastrointestinal symptoms. For most patients with SDH-competent GISTs with a KIT or PDGFR $\alpha$  mutation, treatment consists of surgical resection, with tyrosine kinase inhibition (most commonly imatinib) for unresectable or metastatic disease. Patients with SDH-deficient GIST typically respond poorly to tyrosine kinase inhibition given the absence of these activating mutations. Although the benefit from chemotherapy has not been extensively reported in these patients due to rarity, one case of a SDHD and KIT mutated GIST has been reported that responded well to imatinib.<sup>14</sup> The patient described by Jové et al<sup>15</sup> with familial paraganglioma syndrome type 4, like our patient, was treated with surgical resection only and was free from disease progression at 6 years. However, our patient's mutation has been associated with resistance to imatinib (PMID 18488168).

Follow-up surveillance for GIST depends on the tumor characteristics and the treatment received.<sup>20</sup> If the disease was localized and able to be completely resected, a history and physical as well as abdominal and pelvic CT should be performed every 3 to 6 months for up to 5 years and then annually. We offered this management plan to our patient. If the disease is persistent post treatment, the surveillance should include a history and physical as well as abdominal and pelvic CT every 3 to 6 months indefinitely. A small GIST with no high-risk features on diagnosis should be followed up with endoscopic assessment at 6- or 12-month intervals to determine the need for active treatment.

## Conclusion

This case provides further evidence that mutations in SDHB and KIT are not mutually exclusive with GISTs. It also identifies the need

for endoscopic evaluation for GIST in patients with familial paraganglioma syndrome type 4 with unexplained gastrointestinal symptoms. Additionally, this case emphasizes the importance of complete genetic profiling of all patients with GIST despite the presence of a known somatic SDH mutation or familial paraganglioma syndrome, as identification of KIT/PDGFR mutations may predict response to imatinib and other tyrosine kinase inhibition.

## Disclosure

The authors have no multiplicity of interest to disclose.

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