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Familial Gastrointestinal Stromal Tumor with Germline *KIT* Mutations Accompanying Hereditary Breast and Ovarian Cancer Syndrome

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Abstract. *Background: Familial gastrointestinal stromal tumor (GIST) is a rare disease with germline mutations in the c-kit gene (KIT) or platelet-derived growth factor receptor alpha gene (PDGFRA). We had encountered multiple GISTs in the stomach and small intestine during a screening of ovarian cancer for a woman with hereditary breast and ovarian cancer syndrome (HBOC) with breast cancer susceptibility gene II (BRCA2) mutations. The aim of this study was to examine this case in detail. Case Report: A 65-year-old woman diagnosed with HBOC harboring BRCA2 mutations was found to have multiple tumors in the stomach and small intestine by abdominal screening. All tumors were resected, and KIT gene mutations (p.Trp557Leu and p.Lys558Glu) in exon 11 were detected in all tumors and peripheral blood leukocytes. The patient was diagnosed with familial GIST. Conclusion: This was an extremely rare case in which familial GIST with germline KIT gene mutations co-existed with HBOC.*

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors of the digestive tract and are thought to be derived from interstitial cells of Cajal (ICC), which function as pacemakers for the gastrointestinal tract (1). The most common cause of sporadic GISTs is gain-of-function mutations in c-kit gene (*KIT*) (1), accounting for up to 80-85% of all GISTs, followed by gain-of-function mutations in platelet-derived growth factor receptor alpha gene (*PDGFRA*) (2, 3), accounting for about 10% of all GISTs. The remaining 5-10% include syndromal GISTs associated with multiple tumor syndromes, such as von Recklinghausen disease [neurofibromatosis type 1 (NF1)] or Carney-Stratakis syndrome, harboring germline mutations in the *NF1* and succinate dehydrogenase gene (*SDH*), respectively.

Familial GIST is a familial neoplastic disease with multiple GISTs caused by germline mutations in *KIT* or *PDGFRA*. After the first report by Nishida *et al*. (4), over 30 families have been reported to date. Unlike sporadic GIST, familial GISTs exhibit onset at a younger age but are slow-growing tumors owing to their low malignancy. These tumors are sometimes accompanied by symptoms such as hyperpigmentation, *urticaria pigmentosa*, or dysphagia. Hyperplasia of ICC is observed histologically and, probably with additional mutation, it grows into multiple monoclonal tumors everywhere in the gastrointestinal tract.

Hereditary breast and ovarian cancer syndrome (HBOC) is also a familial neoplastic disease, with multiple malignancies in the breast, ovary, pancreas, prostate, or skin, caused by germline mutations in the DNA-repair genes breast cancer susceptibility gene I (*BRCA1*) and/or breast cancer susceptibility gene II (*BRCA2*). HBOC accounts for 5-10% of total breast cancer cases (5, 6). Despite the wide variety of malignancies accompanied by HBOC, as far as we are aware, no reports have described whether *BRCA1/2* mutations increase the risk of GIST.

We had diagnosed multiple GISTs in the stomach and small intestine during screening for ovarian cancer in a woman with HBOC with *BRCA2* mutations. We detected novel germline mutations in exon 11 (p.Trp557Leu and

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Key Words: KIT mutation, familial gastrointestinal stromal tumor, hereditary breast and ovarian cancer syndrome.

p.Lys558Glu) of the *KIT* gene. These mutations have not been reported previously, and the presence of two different familial neoplastic diseases is extremely rare.

Case Report

The patient was a 65-year-old woman with cancer of the left breast. A family history of HBOC-associated cancer led her to be diagnosed with HBOC with *BRCA2* mutation (Figure 1). Magnetic resonance imaging for ovarian cancer screening revealed multiple tumors in the small intestine. The patient had no digestive symptoms or abnormal skin findings.

After neoadjuvant chemotherapy for breast cancer, partial mastectomy and diagnostic resection of some intestinal tumors were performed. All intestinal tumors were located in the intestinal wall, and no disseminated nodules were found. The tumors were identified as GISTs. The breast cancer characteristics were as follows: invasive ductal carcinoma, estrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor receptor-positive, Ki-67-positive rate of 26.8%, and T2N0M0 stage IIA.

After adjuvant chemotherapy for breast cancer, prophylactic ovariectomy and resection of residual GISTs were performed. Distinct single tumors of the duodenum and small intestine were observed and were found to be a few centimeters in size. In contrast, gastric tumors were smaller, up to 12 mm in size, and presented in a grouped manner. We resected all the tumors except for those in the stomach because gastrectomy was required for complete resection.
All tumors were diagnosed as GISTs. Two years after surgery, there was no progression in computed tomography, even in the gastric region. The patient is being followed-up and is not receiving tyrosine kinase inhibitors.

Histopathology and immunohistochemistry. The specimens resected during surgery were fixed in 10% formalin and embedded in paraffin. Hematoxylin and eosin staining and immunohistochemical staining were performed using antibodies to c-KIT, α-smooth muscle actin (SMA), CD34, S100 protein, and Ki-67.

The maximum size of gastric tumors was 12 mm, and those of the duodenum and small intestine were 7 cm. The tumors were continuous with the proper muscle layer. On hematoxylin and eosin staining, spindle-shaped cells with egg-shaped, or spindle-shaped nuclei were found to grow in bundles (Figure 2A and B). Necrosis was observed in one tumor of the small intestine. The mitotic index was 1 in 50 high-power fields. Gastric tumors were small and multinodular in macro-analysis and consisted of smaller cells than those observed in the small intestine, with hyalinization of the stroma (Figure 2C).

In immunohistochemistry, staining for KIT was diffusely positive in all tumors (Figure 2D), that for CD34 was partially positive in some tumors of the small intestine, while

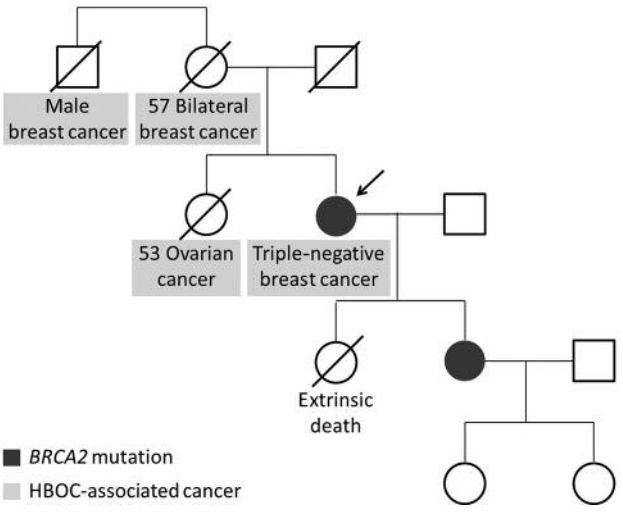

Figure 1. *Hereditary breast and ovarian cancer syndrome (HBOC)-associated family history. The arrow indicates the present case, the female proband. Black shapes indicate breast cancer susceptibility gene II (BRCA2) mutations, and gray shapes indicate HBOC-associated cancer cases. Diagonal lines indicate that the individual is dead, and the numbers are the age in years at the time of death.*

that for α-SMA and S100 protein were negative; the Ki-67 positive rate was 7% (Figure 2E). When assessed according to the modified Fletcher risk classification (7, 8), tumors of the small intestine were high risk, duodenal tumors were low risk, and gastric tumors were very low risk. In addition, hyperplasia of ICC was observed in the myenteric nerve plexus of the small intestine (Figure 2F).

Sequence analysis of the KIT gene. Small blocks of fresh tumor samples were snap-frozen in liquid nitrogen at the time of surgical resection and stored at −80˚C until RNA extraction. Total RNA was extracted with an RNeasy Mini Kit (Qiagen, Inc., Valencia, CA, USA). Complementary DNA was synthesized using reverse transcriptase (Superscript III) and the *KIT* and *PDGFRA* genes were amplified by reverse transcription polymerase chain reaction. DNA was also extracted from peripheral blood leukocytes, and nucleotide sequence analysis was performed. Sequencing was performed as previously described (9).

In all tumors and peripheral blood leukocytes, p.Trp557Leu and p.Lys558Glu *KIT* gene mutations were detected in exon 11 (Figure 3). Additionally, in gastric tumors, the *KIT* gene mutation p.Leu576His was detected in exon 11.

Discussion

Familial GIST is an extremely rare hereditary neoplastic disease with germline gain-of-function mutations in the *KIT*

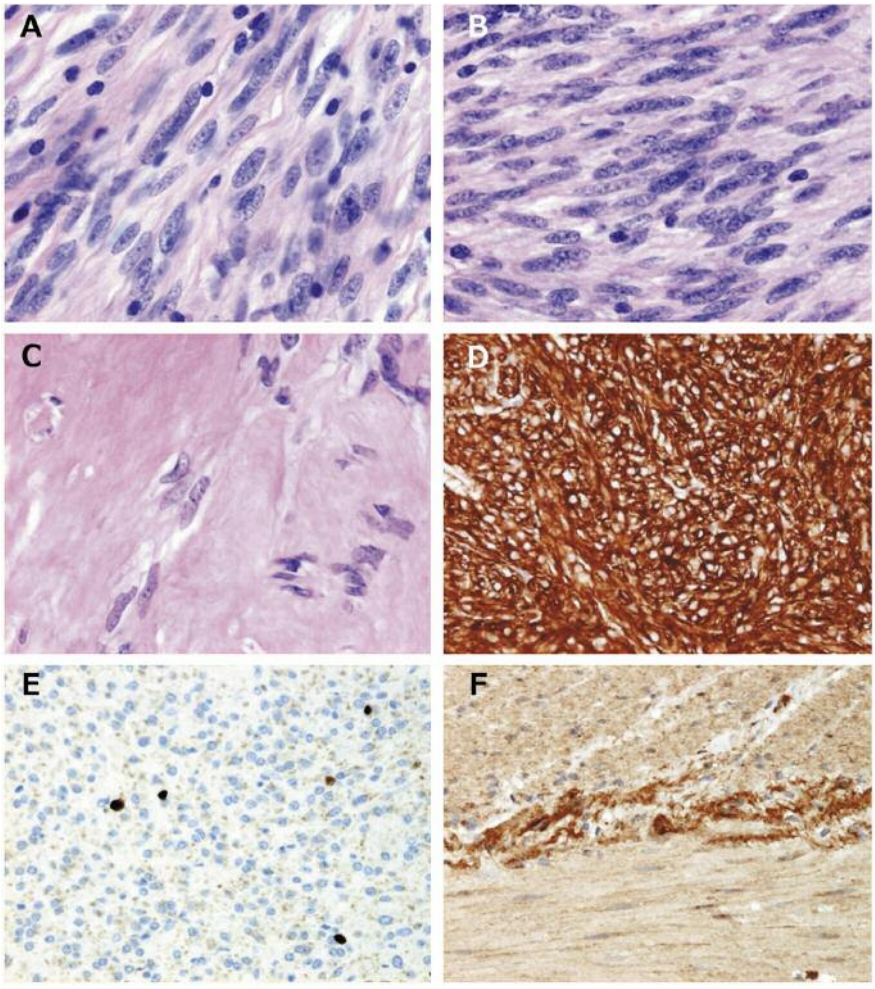

Figure 2. *A: Spindle-shaped cells with egg-shaped or spindle-shaped nuclei grew in groups in the small intestine (hematoxylin & eosin staining). B: Spindle-shaped cells with egg-shaped or spindle-shaped nuclei grew in groups in the duodenum (hematoxylin & eosin staining). C: Gastric tumors consisted of smaller cells than those in the small intestine, with hyalinization of stroma (hematoxylin & eosin staining). D: KIT expression was diffusely positive in the small intestine (KIT staining;). E: The Ki-67-positive rate was 7% in the small intestine (Ki-67 staining). F: Hyperplasia of interstitial cells of Cajal was observed in the myenteric nerve plexus of the small intestine (KIT staining). Original magnification, ×40.*

or *PDGFRA* genes. Including the present case, 36 families with *KIT* gene mutations and four families with *PDGFRA* gene mutations have been reported to date, and the mutation sites observed in this case have not been previously reported (Table I).

About 70-80% of mutation points of sporadic GIST are distributed in exon 11, the juxtamembrane domain of the *KIT* gene. Additionally, 10% are in exon 9, the extracellular domain of the *KIT* gene, and the other 10% are in exon 18, the tyrosine kinase domain II of the *PDGFRA* gene. In familial GISTs, mutations for 22 families (55%) were located in exon 11 of the *KIT* gene, and mutations in eight families (20%) were located in exon 13 of the *KIT* gene. There was no clear correspondence between the site of mutation and the accompanying symptoms. Only one case of breast cancer

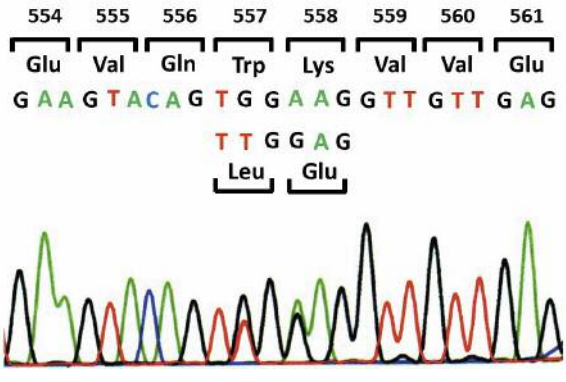

Figure 3. *In all tumor cells and peripheral blood leukocytes, p.Trp557Leu and p.Lys558Glu mutations were detected in exon 11 of the KIT gene.*

Table I. *Familial gastrointestinal stomal tumor cases published in previous studies.*

Author (Ref)	Year	Mutation			Age, years	Gender	Chief complaint	Diffuse hyperplasia of ICC	Hyper-pigmentation	Dysphagia malignancy	Mastocytosis	Other
		Gene	Exon	Protein								
Hartmann *et al.* (10)	2005	*KIT*	8	Asp419del	60	F	Mastocytosis	+	-	+	+	
Speight *et al.* (11)	2013		9	Lys509Ile	35	M	Melena				+	
Nakai *et al.* (12)	2012		11	Tyr553Cys	68	F			-	-	-	
Hirota *et al.* (13)	2000		11	Trp557Arg	69	F	Melena	+		-		
Robson *et al.* (14)	2004		11	Trp557Arg	48	M	Abdominal mass	+	+	+	-	
Maeyama *et al.* (15)	2001		11	Val559Ala	41	F	Abdominal pain		+	-		
Beghini *et al.* (16)	2001		11	Val559Ala	18	M		+	+		+	
Li *et al.* (17)	2005		11	Val559Ala	32	M		+	+	-	+	Melanoma
Kim *et al.* (18)	2005		11	Val559Ala	38	M	Melena	+	-	-	-	
Kuroda *et al.* (19)	2011		11	Val559Ala	25	F	Abdominal pain	+	+		-	
Adela *et al.* (20)	2014		11	Val559Ala					+	+		
Nishida *et al.* (4)	1998		11	Val560del	60	F	Intestinal obstruction		+			
Bamba *et al.* (21)	2015		11	Val560del	43	F	Abdominal pain	-	-	-	-	
Kang *et al.* (22)	2007		11	Val560Gly	65	F	Melena	+	+	-	-	
Wozniak *et al.* (23)	2008		11	Glu575_Pro577 delinsHis	52	M	Melena		-	-	-	
Neuhann *et al.* (24)	2013		11	Leu576Pro	46	M	Routine screening	+	+	+	-	
Carballo *et al.* (25)	2005		11	Leu576_Pro577 insGlnLeu	48	F		+	+		-	
Tarn *et al.* (26)	2005		11	Asp579del	37	F						
Lasota *et al.* (27)	2006		11	Asp579del	58	F						
Kleinbaum *et al.* (28)	2008		11	Asp579del			Abdominal pain	+	+	-	-	
Jones *et al.* (29)	2015		11	Asp579del	40	F	Abdominal pain	+	-	-		
			11	Asp579del	29	F	Screening	+	-	-		
Forde *et al.* (30)	2016		11	Asp579del	46	F	Dyspepsia		+	+		
Isozaki *et al.* (31)	2000		13	Lys642Glu	67	F		+	+			
Graham *et al.* (32)	2007		13	Lys642Glu	57	M	Diarrhea	+	-	-	-	
Vilain *et al.* (33)	2011		13	Lys642Glu	57	M		+	+	-	-	
Peña-Irún *et al.* (34)	2012		13	Lys642Glu								
Wadt *et al.* (35)	2012		13	Lys642Glu	72	M		+				Breast cancer
Bachet *et al.* (36)	2013		13	Lys642Glu								
			13	Lys642Glu								
Yamanoi *et al.* (37)	2014		13	Lys642Tyr	57	F	Abdominal mass	+	-	+		
Hirota *et al.* (38)	2002		17	Asp820Tyr	71	M		+	-	+	-	
O'Riain *et al.* (39)	2005		17	Asp820Tyr	38	M		+	-	+	-	
Veiga *et al.* (40)	2010		17	Asp820Tyr	56	M	Rectal discomfort	+	-	-	-	
Thalheimer *et al.* (41)	2008		17	Asn822Tyr	42	F	Melena	+	-	-	-	
de Raedt *et al.* (42)	2006	*PDGFRA*	12	Tyr555Cys		F	Constipation					
Pasini *et al.* (43)	2007		12	Val561Asp	22	F	Bloody stool					
Ricci *et al.* (44)	2015		14	Pro653Leu	67	M	Abdominal mass					
Chompret *et al.* (45)	2004		18	Asp846Tyr	42	M						
Present case		*KIT*	11	Trp557leu, Lys558Glu	56	F	-	+	-	-	-	Breast cancer

and one case of melanoma have been reported as HBOC-associated malignancies, with the exception of our case.

Notably, the present case was diagnosed in the absence of symptoms. No family history of digestive tract tumors or phenotypic features, such as hyperpigmentation, *urticaria pigmentosa*, or dysphagia, was observed. The mother, sisters, and uncle of our patient had died of HBOC-associated cancer at a relatively young age. In this family, familial GIST may have been masked by more life-threatening HBOC. Despite the fact that there were gastric GISTs remaining in this case,

no signs of growth were detected by computed tomography within a 2-year follow-up, suggesting that tumors grew slowly. Since sporadic GIST with mutations in exon 11 is expected to have good response to imatinib (46), imatinib may be used if the residual tumors begin to show growth in this case.

In the gastric GIST, an acquired mutation in exon 11 of the *KIT* gene was observed in addition to the germline mutation in the *KIT* gene, possibly resulting in the development of multiple tumors that were histologically and macroscopically different from tumors of the small intestine or duodenum. In familial GIST, germline mutations in the *KIT* or *PDGFRA* genes cause polyclonal hyperplasia of ICC, resulting in acquisition of other gene mutations, the development of monoclonal GIST, and the growth and malignant transformation of tumors (47).

Although KIT is always expressed in normal mammary epithelium, KIT expression was previously observed only in 2.4% of breast cancers (43 cases out of 1654 patients), and no *KIT* gene mutations were reported (48). In 171 cases of triple-negative breast cancer, KIT expression was observed in 42.1%, although gain-of-function mutations in the *KIT* gene were detected only in one case (49). These findings suggested that KIT expression may be required for maintenance of the normal mammary epithelium and that gain-of-function mutations in the *KIT* gene do not contribute to tumor growth. Accordingly, tyrosine kinase inhibitors may not be effective, as confirmed by studies showing limited success (50).

Importantly, the KIT signaling pathway is required for the growth and survival of estrogen receptor-negative progenitor cells in the mammary epithelial luminal layer, which is the origin of *BRCA1* mutation-associated breast cancer in mice. However, the cells do not proliferate if KIT is overexpressed. Additionally, overexpression of *Lyn* was found in mice with *BRCA* mutation-associated breast cancer. Lyn is a transducer of the KIT signaling pathway and suppresses BRCA1 (51). These data suggest that *BRCA1* mutations cause dysregulation in the downstream of KIT signaling pathway, resulting in carcinogenesis. Indeed, *BRCA* mutations are a clear risk factor in various malignancies, such as cancer of the breast, ovarian, prostate, pancreas, bladder, bile duct and stomach, and in melanoma. However, there is only one case report of solitary gastric GIST in a patient with a *BRCA2* mutation (52), and no clear risk of GIST in patients with *BRCA* mutations has been reported.

In summary, in the present case, we found two different germline mutations occurring simultaneously, causing different familial neoplastic diseases. The clinical course for this patient may not have contradictions in the natural history of each familial neoplasm. Therefore, this patient needs to be carefully observed during the follow-up period.

References

1 Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y and Kitamura Y: Gain-of-function mutation of c-kit in human gastrointestinal stromal tumors. Science *23*: 577-580, 1998.

2 Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, Singer S, Griffith DJ, Haley A, Town A, Demetri GD, Fletcher CD and Fletcher JA: PDGFRA activating mutation in gastrointestinal stromal tumors. Science *299*: 708-710, 2003.

3 Hirota S, Ohashi A, Nishida T, Isozaki K, Kinoshita K, Shinomura Y and Kitamura Y: Gain-of-function mutation of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology *125*: 660-667, 2003.

4 Nishida T, Hirota S, Taniguchi M, Hashimoto K, Isozaki K, Nakamura H, Kanakura Y, Tanaka T, Takabayashi A, Matsuda H and Kitamura Y: Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. Nat Genet *19*: 323-324, 1998.

5 Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynvh H, Ponder BA, Gayther SA and Zelada-Hedman M: Genetic heterogenity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet *62*: 676-689, 1998.

6 Diez O, Osorio A, Duran M, Martnez-Ferrandis JI, de la Hoya M, Salazar R, Vega A, Campos B, Rodriguez-Lopez R, Velasco E, Chaves J, Diaz-Rubio E, Jesus Cruz J, Torres M, Esteban E, Cervantes A, Alonso C, San Roman JM, Gonzalez-Sarmiento R, Miner C, Carracedo A, Eugenia Armengod M, Caldes T, Benitez J and Baiget M: Analysis of *BRCA1* and *BRCA2* genes in Spanish breast/ovarian cancer patients: a high proportion of mutations unique to Spain and evidence of founder effects. Hum Mutat *22*: 301-312, 2003.

7 Joensuu H: Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol *39*: 1411-1419, 2008.

8 Rutkowski P, Bylina E, Wozniak A, Nowecki Zl, Osuch C, Matlok M, Switaj T, Michej W, Wronski M, Gluszek S, Kroc J, Nasierowska-Guttmejer A and Joensuu H: Validation of the Joensuu risk criteria for primary resectable gastrointestinal stromal tumor – the impact of tumor rupture on patient outcomes. Eur J Surg Oncol *37*: 890-896, 2011.

9 Kinoshita K, Hirota S, Isozaki K, Ohashi A, Nishida T, Kitamura Y, Shinomura Y and Matsuzawa Y: Absence of *c-KIT* gene mutations in gastrointestinal stromal tumours from neurofibromatosis type 1 patients. J Pathol *202*: 80-85, 2004.

10 Hartmann K, Wardelmann E, Ma Y, Merkelbach-Bruse S, Preussner LM, Woolery C, Baldus SE, Heinicke T, Thiele J, Burttner R and Longley BJ: Novel germline mutation of *KIT* associated with familial gastrointestinal stromal tumors and mastocytosis: Gastroenterology *129*: 1042-1046, 2005.

11 Speight RA, Nicolle A, Needham SJ, Verrill MW, Bryon J and Panter S: Rare, germline mutation of KIT with imatinib-resistant multiple GI stromal tumors and mastocytosis. J Clin Oncol *31*: e245-247, 2013.

12 Nakai M, Hashikura Y, Ohkouchi M, Yamamura M, Akiyama T, Shiba K, Kajimoto N, Tsukamoto Y, Hao H, Isozaki K, Hirai T and Hirota S: Characterization of novel germline c-kit gene mutation, KIT-Tyr553Cys, observed in a family with multiple gastrointestinal stromal tumors. Lab Invest *92*: 451-457, 2012.

13 Hirota S, Okazaki T, Kitamura Y, O'Brien P, Kapusta L and Dardick I: Cause of familial and multiple gastrointestinal autonomic nerve tumors with hyperplasia of interstitial cells of Cajal is germline mutation of the *c-KIT* gene. Am J Surg Pathol *24*: 326-327, 2000.

14 Robson ME, Glogowski E, Sommer G, Antonescu CR, Nafa K, Maki RG, Ellis N, Besmer P, Brennan M, Offit K: Pleomorphic characteristics of a germ-line KIT mutation in a large kindred with gastrointestinal stromal tumors, hyperpigmentation, and dysphagia. Clin Cancer Res *10*: 1250-1254, 2004.

15 Maeyama H, Hidaka E, Ota H, Minami S, Kajiyama M, Kuraishi A, Mori H, Matsuda Y, Wada S, Sodeyama H, Nakata S, Kawamura N, Hata S, Watanabe M, Iijima Y and Katsuyama T: Familial gastrointestinal stromal tumor with hyperpigmentation: association with a germline mutation of the *c-KIT* gene. Gastroenterology *120*: 210-215, 2001.

16 Beghini A, Tibiletti MG, Roversi G, Chiaravalli AM, Serio G, Capella C and Larizza L: Germline mutation in the juxtamembrane domain of the kit gene in a family with gastrointestinal stromal tumors and *urticaria pigmentosa*. Cancer *92*: 657-662, 2001.

17 Li FP, Fletcher JA, Heinrich MC, Garber JE, Sallan SE, Curiel-Lewandrowski C, Duensing A, van de Rijn M, Schnipper LE and Demetri GD: Familial gastrointestinal stromal tumor syndrome: phenotypic and molecular features in a kindred. J Clin Oncol *23*: 2735-2743, 2005.

18 Kim HJ, Lim SJ, Park K, Yuh YJ, Jang SJ and Choi J: Multiple gastrointestinal stromal tumors with a germline *c-KIT* mutation. Pathol Int *55*: 655-659, 2005.

19 Kuroda N, Tanida N, Hirota S, Daum O, Hes O, Michal M and Lee GH: Familial gastrointestinal stromal tumor with germ line mutation of the juxtamembrane domain of the *KIT* gene observed in relatively young women. Ann Diagn Pathol *15*: 358-361, 2011.

20 Adela Avila S, Peñaloza J, González F, Abdo I, Rainville I, Root E, Carrero Valenzuela RD and Garber J: Dysphagia, melanosis, gastrointestinal stromal tumors and a germinal mutation of the *KIT* gene in an Argentine family. Acta Gastroenterol Latinoam *44*: 9-15, 2014.

21 Bamba S, Hirota S, Inatomi O, Ban H, Nishimura T, Shioya M, Imaeda H, Nishida A, Sasaki M, Murata S and Andoh A: Familial and multiple gastrointestinal stromal tumors with fair response to a half-dose of imatinib. Intern Med 54: 759-764, 2015.

22 Kang DY, Park CK, Choi JS, Jin SY, Kim HJ, Joo M, Kang MS, Moon WS, Yun KJ, Yu ES, Kang H and Kim KM: Multiple gastrointestinal stromal tumors: Clinicopathologic and genetic analysis of 12 patients. Am J Surg Pathol *31*: 224-232, 2007.

23 Woźniak A, Rutkowski P, Sciot R, Ruka W, Michej W and Debiec-Rychter M: Rectal gastrointestinal stromal tumors associated with a novel germline KIT mutation. Int J Cancer *122*: 2160-2164, 2008.

24 Neuhann TM, Mansmann V, Merkelbach-Bruse S, Klink B, Hellinger A, Höffkes HG, Wardelmann E, Schildhaus HU and Tinschert S: A novel germline *KIT* mutation (p.L576P) in a family presenting with juvenile onset of multiple gastrointestinal stromal tumors, skin hyperpigmentations, and esophageal stenosis. Am J Surg Pathol *37*: 898-905, 2013.

25 Carballo M, Roig I, Aguilar F, Pol MA, Gamundi MJ, Hernan I and Martinez-Gimeno M: Novel *c-KIT* germline mutation in a family with gastrointestinal stromal tumors and cutaneous hyperpigmentation. Am J Surg Pathol *132*: 361-364, 2005.

26 Tarn C, Merkel E, Canutescu AA, Shen W, Skorobogatko Y, Heslin MJ, Eisenberg B, Birbe R, Patchefsky A, Dunbrack R, Arnoletti JP, von Mehren M and Godwin AK: Analysis of *KIT* mutations in sporadic and familial gastrointestinal stromal tumors: therapeutic implications through protein modeling. Clin Cancer Res *15*: 3668-33677, 2005.

27 Lasota J and Miettinen M: A new familial GIST identified. Am J Surg Pathol *30*: 1342, 2006.

28 Kleinbaum EP, Lazar AJ, Tamborini E, Mcauliffe JC, Sylvestre PB, Sunnenberg TD, Strong L, Chen LL, Choi H, Benjamin RS, Zhang W and Trent JC: Clinical, histopathologic, molecular and therapeutic findings in a large kindred with gastrointestinal stromal tumor. Int J Cancer *122*: 711-718, 2008.

29 Jones DH, Caracciolo JT, Hodul PJ, Strosberg JR, Coppola D and Bui MM: Familial gastrointestinal stromal tumor syndrome: report of 2 cases with *KIT* exon 11 mutation. Cancer Control *22*: 102-108, 2015.

30 Forde PM, Cochran RL, Boikos SA, Zabransky DJ, Beaver JA, Meyer CF, Thornton KA, Montgomery EA, Lidor AO, Donehower RC and Park BH: Familial GI stromal tumor with loss of heterozygosity and amplification of mutant *KIT*. J Clin Oncol *34*: e13-16, 2016.

31 Isozaki K, Terris B, Belghiti J, Schiffmann S, Hirota S and Vanderwinden JM: Germline-activating mutation in the kinase domain of *KIT* gene in familial gastrointestinal stromal tumors. Am J Surg Psthol *157*: 1581-1585, 2000.

32 Graham J, Debiec-Rychter M, Corless CL, Reid R, Davidson R and White JD: Imatinib in the management of multiple gastrointestinal stromal tumors associated with a germline *KIT* K642E mutation. Arch Pathol Lab Med *131*: 1393-1396, 2007.

33 Vilain RE, Dudding T, Braye SG, Groombridge C, Meldrum C, Spigelman AD, Ackland S, Ashman L and Scott RJ: Can a familial gastrointestinal tumour syndrome be allelic with Waardenburg syndrome? Clin Genet *79*: 554-560, 2011.

34 Peña-Irún A, Villa-Puente M, García-Espinosa R and Cavadas-López A: Familial gastrointestinal stroma tumor due to mutation in exon 13 (K642E) of the *KIT* gene. Med Clin (Barc) *139*: 512-513, 2012.

35 Wadt K, Andersen MK, Hansen TV and Gerdes AM: A new genetic diagnosis of familiar gastrointestinal stromal tumour. Uqeskr Laeger *174*: 1462-1464, 2012.

36 Bachet JB, Landi B, Laurent-Puig P, Italiano A, Le Cesne A, Lévy P, Safar V, Duffaud F, Blay JY and Emile JF: Diagnosis, prognosis and treatment of patients with gastrointestinal stromal tumour (GIST) and germline mutation of *KIT* exon 13. Eur J Cancer *49*: 2531-2541, 2013.

37 Yamanoi K, Higuchi K, Kishimoto H, Nishida Y, Nakamura M, Sudoh M and Hirota S: Multiple gastrointestinal stromal tumors with novel germline *c-KIT* gene mutation, K642T, at exon 13. Hum Pathol *45*: 884-888, 2014.

38 Hirota S, Nishida T, Isozaki K, Taniguchi M, Nishikawa K, Ohashi A, Takabayashi A, Obayashi T, Okuno T, Kinoshita K, Chen H, Shinomura Y and Kitamura Y: Familial gastrointestinal stromal tumors associated with dysphagia and novel type germline mutation of *KIT* gene. Gastroenterology *122*: 1493-1499, 2002.

39 O'Riain C, Corless CL, Heinrich MC, Keegan D, Vioreanu M, Maguire D and Sheahan K: Gastrointestinal stromal tumors: insights from a new familial GIST kindred with unusual genetic and pathologic features. Am J Surg Pathol *29*: 1680-1683, 2005.
40 Veiga I, Silva M, Vieira J, Pinto C, Pinheiro M, Torres L, Soares M, Santos L, Duarte H, Bastos AL, Coutinho C, Dinis J, Lopes C and Teixeira MR: Hereditary gastrointestinal stromal tumors sharing the *KIT* exon 17 germline mutation p.Asp820Tyr develop through different cytogenetic progression pathways. Genes Chromosomes Cancer *49*: 91-98, 2010.
41 Thalheimer A, Schlemmer M, Bueter M, Merkelbach-Bruse S, Schildhaus HU, Buettner R, Hartung E, Thiede A, Meyer D, Fein M, Maroske J and Wardelmann E: Familial gastrointestinal stromal tumors caused by the novel *KIT* exon 17 germline mutation N822Y. Am J Surg Pathol *32*: 1560-1565, 2008.
42 de Raedt T, Cools J, Debiec-Rychter M, Brems H, Mentens N, Sciot R, Himpens J, de Wever I, Schöffski P, Marynen P and Legius E: Intestinal neurofibromatosis is a subtype of familial GIST and results from a dominant activating mutation in *PDGFRA*. Gastroenterology *131*: 1907-1912, 2006.
43 Pasini B, Matyakhina L, Bei T, Muchow M, Boikos S, Ferrando B, Carney JA and Stratakis CA: Multiple gastrointestinal stromal and other tumors caused by platelet-derived growth factor receptor alpha gene mutations: a case associated with a germline V561D defect. J Clin Endocrinol Metab *92*: 3728-3732, 2007.
44 Ricci R, Martini M, Cenci T, Carbone A, Lanza P, Biondi A, Rindi G, Cassano A, Larghi A, Persiani R and Larocca LM: *PDGFRA*-mutant syndrome. Mod Pathol *28*: 954-964, 2015.
45 Chompret A, Kannengiesser C, Barrois M, Terrier P, Dahan P, Tursz T, Lenoir GM and Bressac-De Paillerets B: *PDGFRA* germline mutation in a family with multiple cases of gastrointestinal stromal tumor. Gastroenterology *126*: 318-321, 2004.
46 von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Casper ES, Conrad III EU, Delaney TF, Ganjoo KN, George S, Gonzalez RJ, Heslin MJ, Kane III JM, Mayerson J, McGarry SV, Meyer C, O'Donnell RJ, Pappo AS, Paz I. B, Pfeifer JD, Riedel RF, Schwartz HS, Van Tine BA, Wayne JD, Bergman MA and Sundar H: Gastrointestinal stromal tumors, version 2.2014. J Natl Compr Canc Netw *12*: 853-862, 2014.
47 Chen H, Hirota S, Isozaki K, Sun H, Ohashi A, Kinoshita K, O'Brien P, Kaousta L, Dardick I, Obayashi T, Okazaki T, Shinomura Y, Matsuzawa Y and Kitamura Y: Polyclonal nature of diffuse proliferation of interstitial cells of Cajal in patients with familial and multiple gastrointestinal stromal tumors. Gut *51*: 793-796, 2002.
48 Simon R, Panussis S, Maurer R, Spichtin H, Glatz K, Tapia C, Mirlacher M, Rufle A, Torhorst J and Sauter G: *KIT* (CD117)-Positive breast cancers are infrequent and lack *KIT* gene mutations. Clin Cancer Res *10*: 178-183, 2004.
49 Zhu Y, Wang T, Guan B, Rao Q, Wang J, Ma H, Zhang Z and Zhou X: *c-KIT* and *PDGFRA* gene mutations in triple-negative breast cancer. Int J Clin Exp Pathol *7*: 4280-4285, 2014.
50 Barton J, Liggett W, Mainwaring M, Hainsworth J, Simons L, Sligel D, Burris III H and Yardley D: Phase II pilot trial of imatinib mesylate with weekly docetaxel in metastatic breast cancer. J Clin Oncol *24*: 10716, 2006.
51 Regan JL, Kendrick H, Magnay FA, Vafaizadeh V and Smalley MJ: c-KIT is required for growth and survival of the cells of origin of *BRCA1*-mutation-associated breast cancer. Oncogene *31*: 869-883, 2012.
52 Waisbren J, Uthe R, Siziopikou K and Kaklamani V: *BRCA1/2* gene mutation and gastrointestinal stromal tumors: a potential association. BMJ Case Rep, 2015. doi: 10.1136/bcr-2014-208830, 2015.

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