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Short Communication

KIT Mutations Are Common in Incidental Gastrointestinal Stromal Tumors One Centimeter or Less in Size

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Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms of the gut wall that express the receptor tyrosine kinase KIT. Somatic mutations that result in constitutive activation of KIT kinase have been identified in a number of studies of GISTs, although the reported frequency of these mutations has varied over a wide range (20 to 92%). Several reports have suggested that *KIT* gene mutations are more common in malignant GISTs than in benign lesions, and it has been proposed that mutations in exon 11 of *KIT* are a negative prognostic factor. To maximize sensitivity for *KIT* mutations we have adapted denaturing high-pressure liquid chromatography as a method for screening polymerase chain reaction amplimers of exons 9, 11, 13, and 17 from GIST genomic DNA. This approach was used to assess the frequency of *KIT* mutations in 13 morphologically benign, incidentally discovered, GISTs identified at autopsy, endoscopy, or laparotomy for unrelated disease. Representing the smallest pathologically recognizable GISTs, these lesions ranged in size from 4 to 10 mm in diameter and were all immunohistochemically positive for KIT. Eleven of the 13 tumors had sequence-confirmed mutations in *KIT*, including 10 mutations in exon 11 (77%) and one mutation in exon 9 (7.7%). The remaining two tumors were wild type for exons 9, 11, and 17; one of these was also analyzed for exon 13 and was wild type in this exon as well. The mutations found in the incidental GISTs were identical to those that have been documented in larger GISTs. In addition, the overall frequency of mutations in the incidental tumors (85%) did not differ significantly from that we previously reported in a series of 72 advanced/metastatic GISTs (86%), strongly supporting the view that activating mutations in *KIT* are acquired very early in the development of most GISTs. The findings suggest that *KIT* mutations per se are of little prognostic importance in GISTs. *(Am J Pathol 2002, 160:1567–1572)*

Gastrointestinal stromal tumors (GISTs) are relatively uncommon mesenchymal neoplasms that arise in the wall of the stomach, small intestine, colon, and other sites within the abdominal cavity.[1] Classification of these neoplasms was a source of controversy for many years, but two key observations published by Hirota and colleagues[2] in 1998 helped to clarify the nature of GISTs. The first observation was that GISTs strongly express the receptor tyrosine kinase KIT (CD117). This marker, which is rarely present on other spindle cell tumors occurring in the abdominal cavity, is now accepted as the most specific immunohistochemical identifier for GISTs.[1,3] The second observation was that mutations were present in the juxtamembrane domain (exon 11) of the *KIT* gene (five of six examined GISTs; 83%), and that these mutations caused constitutive activation of the KIT kinase when expressed in COS cells.[2]

From a number of follow-up studies it is clear that mutations of *KIT* exon 11 are the most common type present in GISTs, but that mutations also occur in exons 9, 13, and 17.[4–14] The mutations vary from single base pair substitutions to complex deletions/insertions, but they are invariably in-frame and in many cases have been documented to cause activation of the KIT kinase independent of its natural ligand, stem cell factor. Correspondingly, phosphorylated (activated) KIT is detectable in extracts of GISTs (M Heinrich, C Corless, and J

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Table 1. PCR Primers Used to Analyze *KIT* Exons

Single step PCR	Forward primer	Reverse primer
Exon 9	ATGCTCTGCTTCTGTACTGCC	CAGAGCCTAAACATCCCCTTA
Exon 11	CCAGAGTGCTCTAATGACTG	ACCCAAAAAGGTGACATGGA
Exon 13	CATCAGTTTGCCAGTTGTGC	ACACGGCTTTACCTCCAATG
Exon 17	TGTATTCACAGAGACTTGGC	GGATTTACATTATGAAAGTCACAGG

Nested PCR	Forward primer	Reverse primer	Second forward primer	Second reverse primer
Exon 9	AGCCAGGGCTTTTGTTTTCT	CAGAGCCTAAACATCCCCTTA	ATGCTCTGCTTCTGTACTGCC	CCTTTGTTGTTACCTTTAAATGC
Exon 11	CCTTTGCTGATTGGTTTCGT	AAACAAAGGAAGCCACTGGA	CCAGAGTGCTCTAATGACTG	ACCCAAAAAGGTGACATGGA
Exon 13	GTTCCTGTATGGTACTGCATGCG	CAGTTTATAATCTAGCATTGCC	CATCAGTTTGCCAGTTGTGC	ACACGGCTTTACCTCCAATG
Exon 17	GGTTTTCTTTTCTCCTCCAACC	GGATTTACATTATGAAAGTCACAGG	TGTATTCACAGAGACTTGGC	GAAACTAAAAATCCTTTGCAGGAC

Fletcher, manuscript submitted).[12] Activation of KIT seems important to the growth of GISTs, because the proliferation of GIST cells in culture is inhibited by the tyrosine kinase inhibitor STI571, a potent blocker of KIT kinase activity.[15] Moreover, in recent clinical trials the majority of patients with malignant GIST have shown a benefit to treatment with STI571.[16–18]

Although the importance of KIT mutations in the biology of GISTs is well established, it remains unclear at what point in the development of these tumors the mutations are acquired. Several studies have suggested that mutations in *KIT* exon 11 are more common in malignant than in benign GISTs.[5,6,14,19,20] In a large series published by Taniguchi and colleagues[7] (124 patients), exon 11 mutations were identified in 57% of tumors and seemed to correlate with disease recurrence and shortened survival (86% *versus* 49% 5-year survival). In contrast, Rubin and colleagues[12] did not observe a correlation between *KIT* mutation status and tumor grade.

In this report we examine the frequency of *KIT* gene mutations in a series of tumors that were small (10 mm or less), clinically incidental, and morphologically benign. The majority of these lesions, which represent the earliest pathologically recognizable GISTs, were found to harbor mutations of the type frequently identified in larger, malignant lesions. The results favor the view that activating mutations in *KIT* occur early in the development of GISTs.

Materials and Methods

One hundred twenty GISTs were identified in the pathology archives of the Oregon Health and Science University Hospital, the Portland VA Medical Center, and the Northwest Kaiser Permanente Regional Laboratory by searching for cases coded as "leiomyoma," "leiomyosarcoma," or "sarcoma, NOS" in association with abdominal organs (excepting uterus). Fifteen tumors were incidentally discovered lesions; 13 of these were 1.0 cm or less in size and these were selected for further study, following the institutional review board regulations of all three source institutions.

Immunohistochemistry for KIT (CD117) was performed as follows. Sections from the original paraffin blocks were heated in Citra buffer (Biogenex, San Ramon, CA) for 20 minutes in a vegetable steamer (Sunbeam-Oster Household Products, Schaumburg, IL) and then placed on a DAKO automated immunostainer (DAKO Corp., Carpinteria, CA). A standard avidin-biotin staining protocol was performed with the DAKO polyclonal rabbit antibody (DAKO A4502), used at 1:400 dilution, goat biotinylated anti-rabbit secondary (Vector Laboratories, Burlingame, CA), and the Vectastain Elite kit (Vector Laboratories). Endogenous mast cells served as internal-positive controls in all cases; the antibody did not stain other tissue elements (eg, epithelial cells) at the selected titer.

Tumor tissue was identified on unstained, 5 μm sections by comparison with hematoxylin and eosin (H&E)-stained slides and was carefully collected using a clean, sterile scalpel blade into a microfuge tube. Because the tumors were round discrete masses, dissection by this approach was straightforward and there was minimal contamination from adjacent normal muscularis cells (note that such contamination would serve to bias the results toward an apparent wild-type genotype). The dissected tissue was deparaffinized by serial extraction with xylenes and ethanol and allowed to air-dry. DNA was extracted using the Qiagen minikit (no. 51304; Qiagen, Valencia, CA) in accordance with the manufacturer's recommendations.

Purified tumor DNA (0.5 μg) was subjected to 45 cycles of polymerase chain reaction (PCR) using the High-Fidelity PCR System (no. 1732078; Roche, Indianapolis, IN). Primer pairs for each exon analyzed are listed in Table 1. Negative controls were included in every set of amplifications. In a minority of cases there was insufficient amplified DNA for screening by high-pressure liquid chromatography (HPLC) after single step amplification and therefore a second round of amplification was performed using nested primers (Table 1).

Aliquots (5 to 20 μl) of the final PCR reaction were screened for mutations on a Transgenomic WAVE HPLC system (D-HPLC; Transgenomic, Inc., Omaha, NE) by running at nondenaturing (50°C) or partially denaturing temperature (exon 11, 56°C; exon 13, 59°C; exon 17, 58°C). D-HPLC-detected mutations were confirmed by two methods: 1) re-amplification of the exon and repeat D-HPLC analysis on a different day; 2) bi-directional sequence analysis on an ABI 377 sequencer using the BigDye terminator kit (Applied Biosystems, Inc., Foster City, CA).

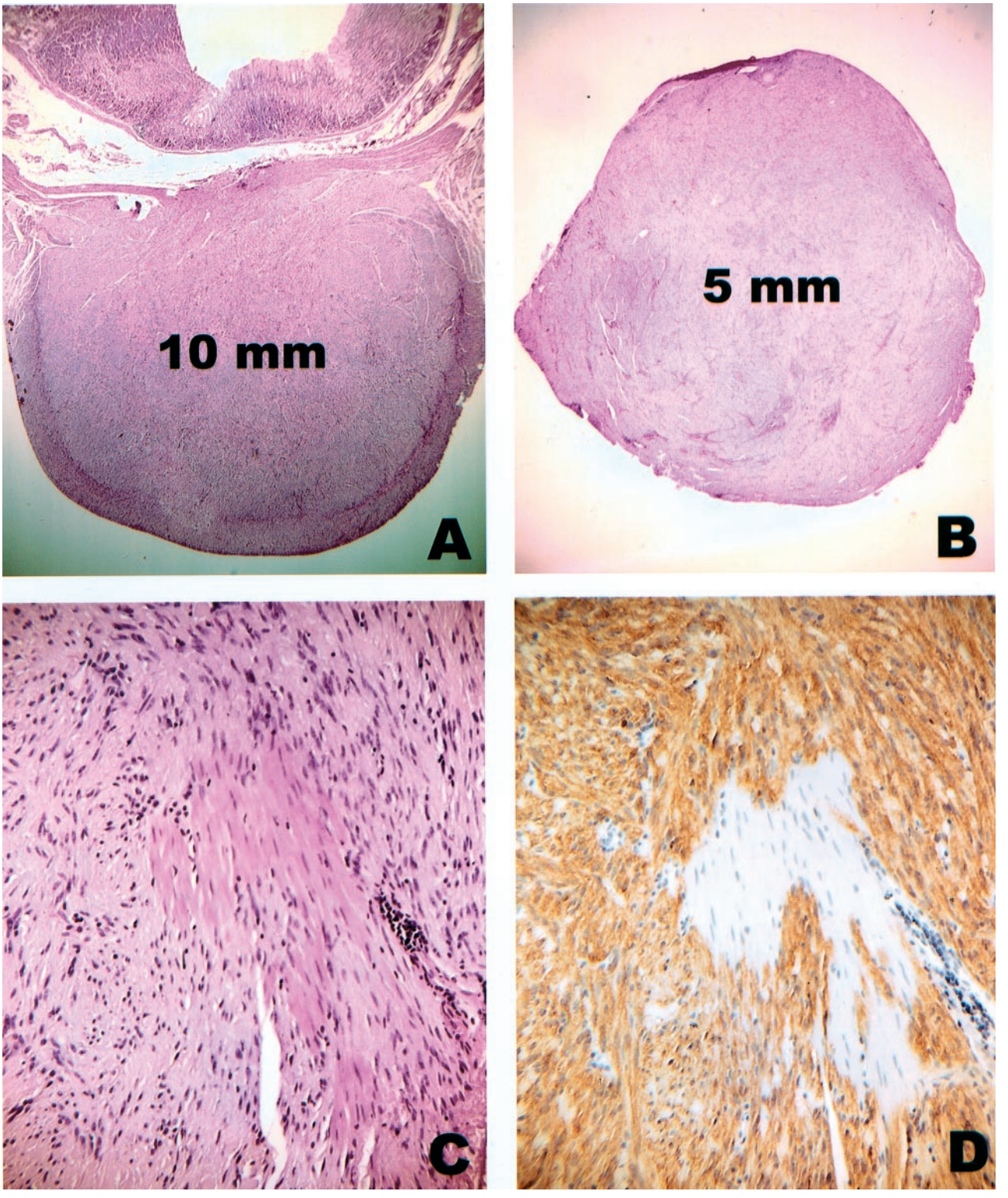

Figure 1. Incidental GISTs. **A:** H&E-stained section of case 6 showing a 10-mm tumor centered in the muscularis propria of the stomach. The lesion was discovered during a gastroesophagectomy for a large esophageal leiomyoma. **B:** H&E-stained section of case 11 showing a well-circumscribed 5-mm nodule that was removed from the serosal aspect of the small bowel during surgery for endometrial adenocarcinoma. **C:** Close-up of case 11. Note that entrapped smooth muscle cells of the muscularis propria are morphologically similar to the tumor cells. **D:** Same area of case 11 as in **C**, immunostained for KIT. The tumor cells are strongly positive whereas the smooth muscle cells are negative.

Table 2. Incidental GISTs

Case	Sex/age	Size	Location	How discovered	*KIT* mutation
1	F/88	9 mm	Stomach	Surgery for ovarian cystadenoma	Exon 11
2	M/53	10 mm	Small intestine	Exploratory laparotomy (lymphoma)	Exon 11
3	M/56	<10 mm	Stomach	Autopsy (massive pulmonary emboli)	Exon 11
4	M/45	6 mm	Rectum	Incidental finding at endoscopy	Exon 11
5	M/76	4 mm	Stomach	Surgery for esophageal adenocarcinoma	Exon 11
6	F/48	10 mm	Stomach	Surgery for large esophageal leiomyoma	Exon 11
7	M/65	7 mm	Stomach	Surgery for gastric adenocarcinoma	Exon 11
8	F/78	10 mm	Stomach	Vagotomy for unrelated gastric ulcer disease	Exon 11
9	F/65	8 mm	Small intestine	Surgery for villous adenoma of colon	Exon 11
10	M/60	6 mm	Stomach	Incidental finding at endoscopy	Exon 11
11	F/62	5 mm	Small intestine	Surgery for endometrial adenocarcinoma	Exon 9
12	M/64	5 mm	Stomach	Incidental to gastric polyp resection	None detected
13	F/80	5 mm	Stomach	Autopsy (myelodysplastic syndrome)	None detected

Case 9 was heavily infiltrated by lymphocytes and yielded only a small mutant peak at the nondenaturing temperature when its exon 11 amplimer was analyzed by D-HPLC. Although this peak suggested the presence of a deletion, the quantity of mutant DNA was too small to be confirmed by direct sequencing. Therefore the amplification products were cloned into pCR4-TOPO using the TOPO TA cloning kit (version H; Invitrogen, Carlsbad, CA) and the ligated plasmids were used to transform competent *Escherichia coli* (OneShot TOP10, Invitrogen). Isolated plasmids were screened for the mutant exon insert by PCR and D-HPLC. Direct sequence analysis of cloned mutant DNA confirmed the presence of an in-frame exon 11 deletion in this case.

Results and Discussion

In a series of 120 GISTs identified from the pathology archives of three Portland area hospitals, there were 15 tumors that were clinically inapparent and were discovered incidentally at the time of surgery, endoscopy, or autopsy. Two of these tumors were >1 cm in greatest diameter (3.2 cm and 2.7 cm) and had negative prognostic features (>5 mitoses per 50 high-power fields, necrosis); these were excluded from the study. The remaining 13 tumors ranged in size from 4 to 10 mm, were morphologically benign, and lacked mitoses on routine H&E-stained sections (Figure 1; A to C). Two of the tumors represented incidental findings at autopsy, two were discovered during endoscopy, and the remaining nine were identified at laparotomy performed for unrelated disease (Table 2). In all cases, the tumor cells stained positively for KIT by immunohistochemistry (Figure 1D).

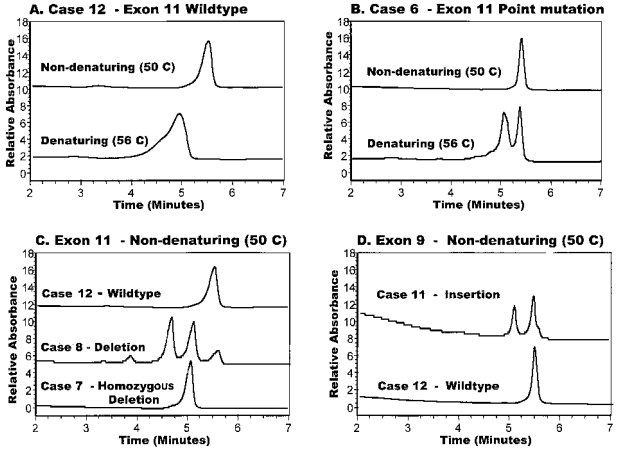

Figure 2. D-HPLC elution profiles of *KIT* exon amplimers. **A:** Wild-type exon 11 amplimer (case 12) run at denaturing and nondenaturing temperatures. **B:** Exon 11 amplimer containing a point mutation (case 6) is resolved from wild-type amplimer at the denaturing temperature. **C:** Comparison of the elution profiles for exon 11 amplimers representing pure wild-type sequence (case 12), pure deletion mutation (case 7), and a mixture of wild-type and deletion mutations (case 8). In the latter case there are four separate peaks that represent homotypic and heterotypic combinations of mutant and wild-type strands after re-annealing. **D:** The exon 9 insertion mutation discovered in case 11 has a distinctive elution pattern in comparison with the wild-type amplimer from case 12.

Genomic DNA prepared from each of the 13 incidental tumors was subjected to PCR amplification of exon 11 of the *KIT* gene, yielding a 236-bp product that was screened for the presence of a mutation on a modified HPLC system (D-HPLC) run at nondenaturing and partially denaturing temperatures. Ten tumors (77%) demonstrated aberrant D-HPLC profiles for exon 11, as illustrated in Figure 2, B and C. The corresponding mutations found by direct sequencing are listed in Table 3. Three were point mutations and the remainder consisted of deletions with or without small substitutions. Each of these mutations was confirmed by D-HPLC analysis of a repeat amplification from the original tumor DNA; in some cases, the DNA sequence analysis was also repeated. All of these mutations have been observed in larger, clinically significant GISTs (M Heinrich et al, manuscript in preparation).[17] Figure 2C illustrates a tumor (case 7) in which the deletion mutation was detected but the wild-type allele was not. The locus or chromosome bearing the wild-type allele in this case, as well as that in case 4, was apparently lost. Detection of such events in subclinical GISTs suggests that there may be a selective advantage to down-regulating wild-type KIT expression in the presence of a KIT mutation.

Tumors that were negative for exon 11 mutations were further analyzed for mutations in exon 9 of *KIT* by the combination of D-HPLC and direct sequencing. Case 11 reproducibly yielded an AY duplication/insertion in this exon (Figure 2C; Table 3). This mutation has been observed in several recent studies of GISTs and has been

Table 3. Mutations Detected in Incidental GISTs

Case	Exon 11	Exon 9	Exon 13	Exon 17
1	Deletion KVVEEING 558–565 R*	–	–	–
2	Point mutation V559D*	–	–	–
3	Deletion KPMYEVQWK 550–558*	–	–	–
4	Deletion D570 (homozygous)*	–	–	–
5	Deletion NYVYIDPTQL 567–576 KV*	–	–	–
6	Point mutation V560D*	WT^{DHPLC}	–	–
7	Deletion QKPMYEVQWK 549–558Q (homozygous)*	WT^{DHPLC}	WT^{DHPLC}	WT^{DHPLC}
8	Deletion KPMYEVQWK 550–558*	WT^{DHPLC}	–	–
9	Deletion YIDPTQLPY 570–578*	WT^{DHPLC}	–	–
10	Point mutation V559D*	WT^{DHPLC}	–	–
11	WT^{DHPLC}	Insertion AY 502–503*	–	–
12	WT*	WT^{DHPLC}	WT^{DHPLC}	WT^{DHPLC}
13	WT*	WT^{DHPLC}	–†	WT^{DHPLC}

*Sequence confirmed.
†Insufficient DNA available ^{DHPLC} denaturing HPLC.
–, Not done.

shown to cause constitutive activation of KIT.[8,11,13,21] The other two tumors showed wild-type profiles for all exons examined (insufficient DNA was available to allow exon 13 analysis on one of these tumors). It remains possible that both of these tumors harbor a mutation elsewhere in the *KIT* gene.

The issue of whether *KIT* mutations are related to the oncological progression of GISTs has been raised in several studies, with differing results. Lasota and coworkers[6] found only one exon 11 mutation in 19 benign GISTs (5.2%), whereas 12 of 24 malignant GISTs (50%) harbored detectable mutations. Similarly, Li and colleagues[20] reported exon 11 mutations in 3 of 4 borderline tumors and 6 of 10 malignant tumors, but found no mutations in the 2 benign lesions examined. This apparent difference between benign and malignant GISTs was not as pronounced in the study by Debiec-Rychter and colleagues[14] that included sequencing of exons 9 and 13. They observed KIT mutations in 3 of 9 (33%) benign tumors and 8 of 14 (57%) malignant tumors.

Using a reverse transcriptase-PCR approach, Rubin and colleagues[12] recently documented *KIT* mutations in 10 of 10 benign GISTs (100%), paralleling the results reported here. Indeed, there was no difference in the *KIT* mutation frequency among the benign, borderline, and malignant tumors examined by Rubin and colleagues,[12] (total 48 cases), and the overall incidence of mutations was strikingly high (92%). The data from this study suggest that technical issues may influence the detection of *KIT* mutations in genomic DNA, reducing the apparent mutation frequency. In a recent analysis of genomic DNA from 72 malignant GISTs, we used D-HPLC to screen PCR amplimers of the *KIT* gene and found mutations (sequence-confirmed) in 86% of cases, which is quite close to the frequency observed by Rubin and colleagues[17] using reverse transcriptase-PCR. Based on our experience, there are two advantages of using D-HPLC to screen PCR amplimers. First, D-HPLC screening predicts the type of mutation to be expected during DNA sequence analysis. Second, there is increased sensitivity for mutations (<10% mutant DNA can be detected). This is illustrated by case 9, in which a minor peak representing an exon 11 deletion was reproducibly detected but could not be confirmed by direct sequence analysis. Contaminating wild-type DNA from infiltrating lymphocytes likely interfered with the sequence analysis, although it is also possible that only a minority of the tumor cells harbored the mutation. Subcloning of the mutant peak yielded sufficient mutant amplimer to document the in-frame deletion in this case.

In applying the D-HPLC approach to the incidental tumors in this report, we detected exon 11 mutations in 77% (10 of 13), matching the 70% frequency that we observed among the 72 malignant GISTs. Moreover, the overall percentage of *KIT* mutations in the group of incidental tumors (85%) was essentially identical to that of the malignant GISTs (86%). It has previously been suggested that GISTs harboring an exon 11 mutation have a worse prognosis than tumors without detected mutations.[7,19] However, the relatively low overall frequency of *KIT* mutations observed in these studies (37 to 57%) complicates the interpretation of their findings.

In the course of selecting incidental GISTs for this study, we identified several small leiomyomas of the type recently reviewed by Miettinen and colleagues.[22] These lesions, which are often associated with the muscularis mucosae, may have areas of hyalinization and other morphological features that closely resemble low-grade GISTs on H&E stain. Nevertheless, they are immunohistochemically negative for KIT and are usually positive for desmin. We examined one small leiomyoma for *KIT* mutations and found none (data not shown).

The presence of activating *KIT* mutations in a high percentage of early, benign GISTs is entirely consistent with the proposal that these mutations represent a gatekeeper alteration that plays a fundamental role in GIST development. It is also consistent with recent studies of four different kindreds in which heritable mutations of *KIT* exon 11 or 13 have been demonstrated.[23–26] In all four kindreds, affected individuals develop multiple GISTs, and in some of these patients there is demonstrable hyperplasia of *KIT*-positive cells in the area of Auerbach's plexus, consistent with interstitial cells of Cajal.

In summary, we have examined 13 clinically incidental, morphologically benign GISTs that were 10 mm or less in size and found an 85% incidence of mutations in the *KIT* gene. This high frequency of mutations is strikingly similar to that observed by the same methodology in a larger series of clinically significant GISTs, suggesting that these mutations occur very early in the course of GIST development. Our findings do not support a negative prognostic impact of *KIT* mutations, as has been proposed in other studies.

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