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Original Article

Analysis of clinicopathologic features and gene mutations in gastrointestinal stromal tumor: a series of 58 patients

Hao Cheng, Tian Qiu, Su-Sheng Shi

Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

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Abstract: Background: In gastrointestinal stromal tumor (GIST), mutually exclusive gain-of-function mutations of c-kit and PDGFRα are associated with different mutation-dependent clinical features. We analyzed clinico-pathologic features and genotypes of GIST among patients in China. Methods: Adult patients with GIST in the stomach, small intestine, colorectum, or extra-gastrointestinal areas were enrolled in this study. These patients had been subjected to surgical resection without imatinib (Gleevec) treatment at the Cancer Hospital, Chinese Academy of Medical Sciences from January 2009 to January 2019. Samples were obtained for histopathologic examination. Mutations in c-kit and PDGFRα genes were analyzed by PCR and next generation sequencing (NGS). Clinico-pathologic characteristics of each gene were also analyzed. Results: A total of 58 GIST patients was enrolled in this study. In terms of genotypes, there were 51 (87.9%) c-kit mutations, 5 (8.6%) PDGFRα mutations, and 2 (3.4%) wild-type mutations. In terms of cell types, there were 40 cases (69.0%) with spindle cell type, 3 cases (5.2%) with epithelioid cell type and 3 cases (5.2%) with mixed spindle-epithelioid cell type. Among the 4 mutant forms of c-kit exon-11, the most common were point mutations in 16 cases (38.1%), deletion mutations in 13 cases (31.0%), insertion mutations in 4 cases (9.5%), and mixed mutations in 9 cases (21.4%). Based on risk grade classification of the National Institutes of Health (NIH), 3 cases (5.2%) were very-low risk, 9 cases (15.5%) were low risk, 19 cases (32.8%) were medium risk, and 23 cases (39.7%) were high risk. Significant differences in cell type were identified across different gene types (P = 0.022). Similarly, differences in tumor risk were found among different mutant forms of c-kit gene exon-11 (P = 0.039). Conclusion: With c-kit mutations, spindle cell type prevalence exceeded that of the epithelioid cell type and mixed spindle-epithelioid cell type. Spindle and mixed spindle-epithelioid cell types were the most prevalent in the category of PDGFRα mutations. In wild type cases, spindle and epithelioid cell types were the most common. A high risk of deletion and mixed mutations, and intermediate risk of point and insertion mutations were observed in c-kit exon-11 mutation type.

Keywords: Gastrointestinal stromal tumor, mutations, c-kit, PDGFRα

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. More than 85% of GISTs occur due to mutations in gene receptor tyrosine kinases (c-kit) and platelet-derived growth factor receptor (PDGFRα) [1]. Approximately, 15% of adults and 85% of children with GISTs lack mutations in c-kit and PDGFRα. Such cases are referred to as Wild-Type (WT) GISTs [2]. The most common exons for c-kit gene mutations are exon 9, 11, 13, and 17, with c-kit exon-11 mutations being the most active [3].

Mutations in the PDGFRα gene occur in about 10% of GIST patients, and the most common type of mutation is the exon-18 D842V point mutation, accounting for more than 90% of all PDGFRα mutation types [4]. C-kit mutations are associated with liver metastasis and poor tumor prognosis [5]. The PDGFRα mutation is associated with suppressed nuclear mitosis and malignancy, suggesting this mutation is a marker for good prognosis [6, 7].

The clinical significance of mutations in GIST has not been conclusively determined. In this study, we retrieved clinical records of adult

patients whose GISTs were located in the stomach, small intestine, colorectum or extra-gastrointestinal area. These patients had been subjected to surgical resection without imatinib (Gleevec) treatment at the Cancer Hospital, Chinese Academy of Medical Sciences from January 2009 to January 2019. The retrieved clinical records were used to investigate c-kit/PDGFRα gene mutations and their relationships to biologic features.

Materials and methods

Patients and samples

Patients with primary GIST (n = 58) who underwent complete resection at the Cancer Hospital, Chinese Academy of Medical Sciences from January 2009 to January 2019 were enrolled in this study. Those with multiple focal GISTs, pediatric GISTs, familial GISTs, neurofibromatosis type-I, and Carney triad were excluded. None of the patients had been received imatinib before surgery.

DNA extraction

Samples were fixed in 10% neutral buffered formalin for 16-48 h, and then were embedded in paraffin. Tissue blocks with adequate tumor cellularity (≥20%) were assessed by an expert pathologist (Dr. Su-sheng Shi). DNA was extracted from selected blocks using the QIAamp DNA formalin-fixed and paraffin-embedded (FFPE) Tissue Kits (Qiagen, Germany), according to the manufacturer's instructions. Qubit 2.0 Fluorometer (Thermo Fisher Scientific, Carlsbad, CA, USA) was used to determine DNA quantity.

Construction and sequencing of the DNA library

About 10 ng of DNA was used to construct the amplicon DNA library. DNA was amplified by PCR and ligated to different barcodes. Libraries for all samples were mixed and clonally amplified onto the IonSpheres (ISP). Subsequently, they were enriched on the IonOneTouch system to prepare DNA templates using the Ion PGM (TM) Hi-Q (TM) OT2 Kit (Thermo Fisher). Finally, enriched ISPs were added onto a 318 Chip and sequenced on the Ion Torrent PGM platform using the Ion PGM HI-Q SEQ Kit (Thermo Fisher), according to the manufacturer's instructions.

Sequence data analysis

Sequencing data from PGM runs were generated using the Torrent Suite Software. Initial variant calling was filtered by comparing the 1000 Genomes data to GRCh 37. Mutations were designated and annotated using the Torrent Variant Caller. Mutations were identified when coverage depth ≥1000 reads and mutant allele frequency ≥5%. All mutations were further visually examined using the Integrative Genomics Viewer.

Ethical approval

Ethical approval was obtained from the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China (Approval number: 21/135-2806). This study was conducted in accordance with the Declaration of Helsinki. The information involved in this study was retrospectively retrieved from the electronic recording system of our hospital and did not contain any personal information of participants. Therefore, the requirement for patient consent was waived, and all data from cases were anonymized or maintained confidentially.

Statistical analysis

Data were statistically analyzed using the SPSS 21.0 software. Categorical variables were expressed as frequencies. The Chi-square or Fisher's exact probability tests were used to compare groups. Correlation analyses were performed by association analysis of unordered categorical variables. First, a chi-square test of independence of two attributes was performed according to the linked list of cross-classification counts. Then, the correlation coefficient was calculated. $P \leq 0.05$ was considered significant.

Results

Clinic-pathological features of participants

Of the 58 GIST patients, 29 were male (50%) and 29 were female (50%). Their ages ranged from 20 to 87 years, with a median age of 57.5 years. Thirty cases (51.7%) had primary tumor in the stomach, 16 cases (27.6%) in the small intestine, 3 cases (5.2%) in the colorectal area, and 9 cases (15.5%) in extra-gastrointestinal areas (including the abdominal, pelvic, and

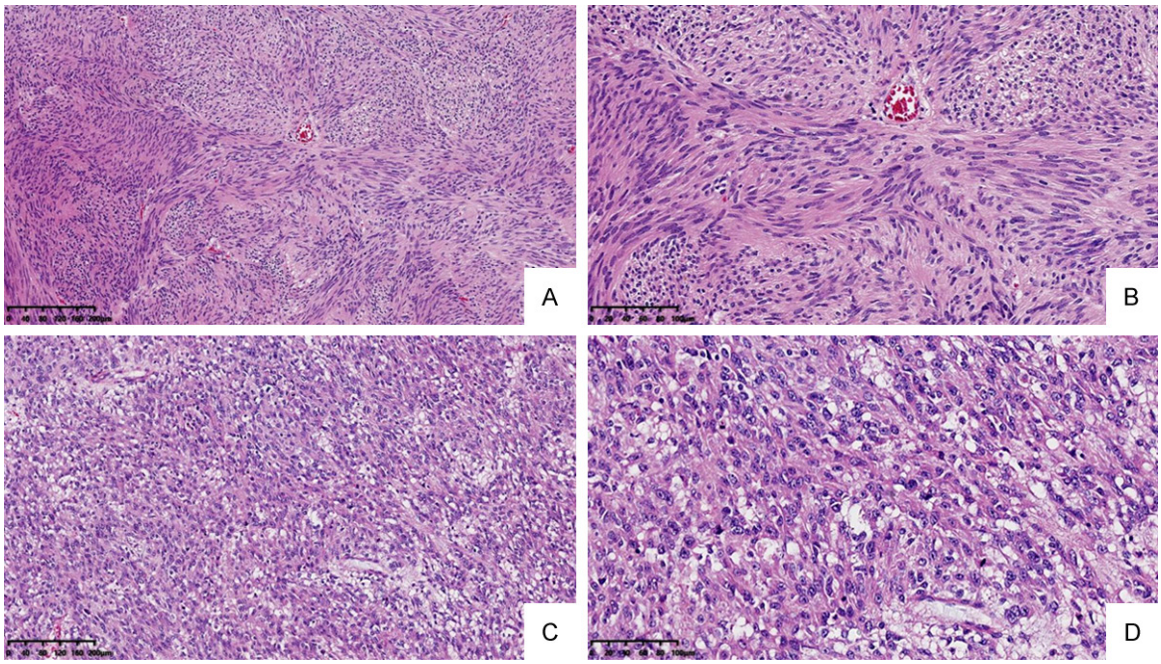

Figure 1. Microscopic examination of GIST. A. Spindle cell type (magnification, ×100). B. Spindle cell type (magnification, ×200). C. Epithelioid cell type (magnification, ×100). D. Epithelioid cell type (magnification, ×200).

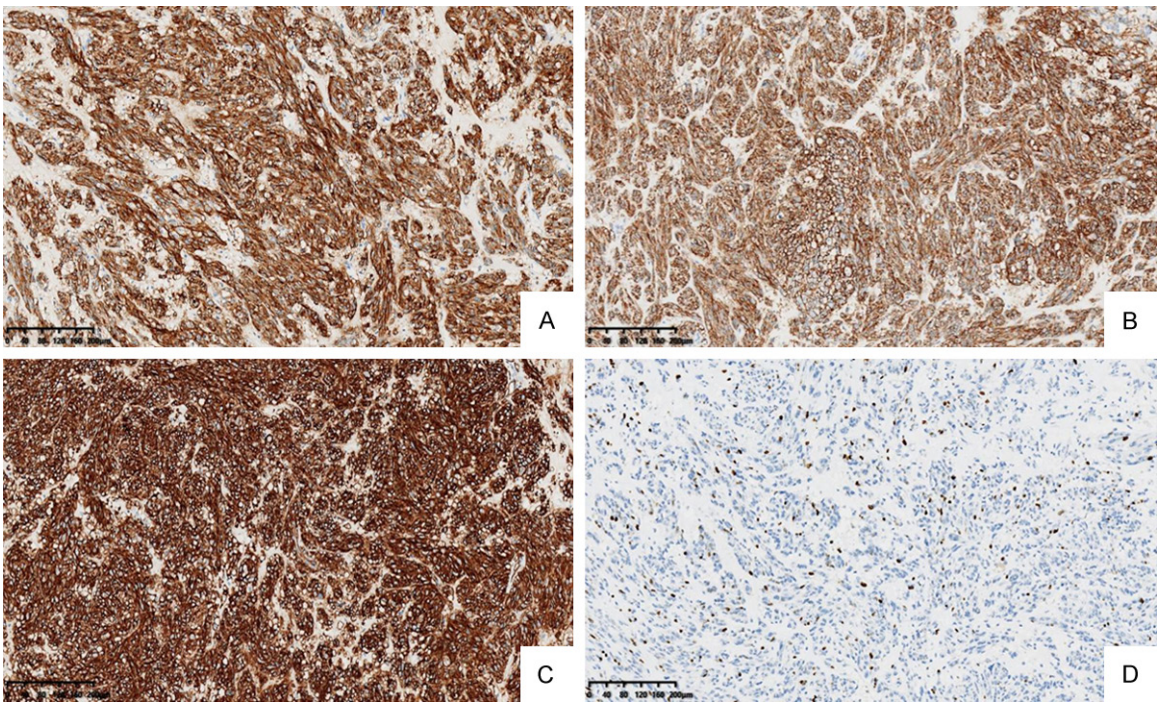

Figure 2. Immunohistochemical markers of GIST. A. CD117 was positive in neoplastic cells (magnification, ×100). B. DOG-1 was positive in neoplastic cells (magnification, ×100). C. CD34 was positive in neoplastic cells (magnification, ×100). D. Ki-67 staining rate was 15% (magnification, ×100).

peritoneal cavities). There were 40 cases (69.0%) with spindle cell type, 3 cases (5.2%) with epithelioid cell type (**Figures 1**, **2**), 3 cases (5.2%) with mixed spindle-epithelioid cell type,

and data for 12 cases (20.7%) were not available. There were 35 cases (60.3%) with mitotic counts ≤ 5/50HPF, 17 cases (29.3%) with >5/50HPF, and 6 cases (10.3%) with missing data.

Tumor diameters in the entire cohort were in the range of 0.7~15.0 cm, with a median diameter of 5.5 cm. 5 cases (8.6%) had tumor size ≤2 cm, 19 cases (32.8%) had >2 to ≤5 cm, 23 cases (39.7%) were >5 to ≤10 cm, 9 cases (15.5%) were >10 cm, and 2 cases (3.4%) lacked data on tumor size. According to the classification by the United States National Institutes of Health (NIH) [8], GIST risk is divided into very-low risk, low risk, intermediate, and high risk. 3 cases were categorized as very-low risk (5.2%), and 9 as low-risk (15.5%), 19 as intermediate risk (32.8%) and 23 as high-risk cases (39.7%). Data for 4 cases (6.9%) were not available. Positive rates of CD117, DOG-1, and CD34 were 96.6%, 96.6%, and 93.1%, respectively. For a Ki-67 index of ≤5%, 5-10%, and ≥10%, there were 24 cases (47.1%), 8 cases (15.7%), and 19 cases (37.3%), respectively. 4 cases (6.9%) had concurrent metastasis.

Genetic mutations

A total of 51 cases (87.9%) with c-kit gene mutations were detected. Exon-11 of c-kit gene mutations were the most common with 42 cases (82.4%), of which W557_K558del (6 cases, 14.3%) and W557R (6 cases, 14.3%) were prevalent. Among the 13 cases with c-kit exon-11 deletion mutations, 2 cases (4.8%) had one codon deletion, while 11 cases (26.2%) had ≥2 codon deletions, among which 2 cases (4.8%) had large fragment deletions involving codons 557-558. There were 16 point mutation cases involving codons 557, 559, and 560. Moreover, codon 559 was the most prevalent, occurring in 7 (16.7%) of the 16 cases.

Exon-9 mutation was found in 7 cases (13.7%), with only one type of insertion mutation (all Y503_F504insAY), with 5 cases occurring in the small intestine, and 2 cases in the stomach and esophagus. Among the 7 cases, 4 were high risk (3 in the small intestine, one in the stomach). Exon-13 mutation was found in one case (2%), and the mutation type was a point mutation (K642E) in codon 642. The case with exon-13 mutation in the rectum was high risk.

There were 5 cases (8.6%) of PDGFR mutation (all exon-18 mutations), including four cases of D842V mutations and one case of I843_846delIMHD mutation in the stomach (**Figure 3**). Exon-12 and 14 mutations were not detected.

Relationship between gene mutation type and clinico-pathologic characteristics

As shown in **Table 1**, there were significant differences in cell types among different gene types. For c-kit genes, the spindle cell type was the most common, accounting for 72.55%. In the PDGFRα gene, the spindle and mixed spindle-epithelioid cell types were the most prevalent, each accounting for 40%. Among the wild types, the spindle and epithelioid cell types were the most common, each accounting for 50%.

Table 2 shows that there were significant differences in tumor risk among different c-kit gene exon-11 mutation types. Among the deletion mutation types, high risk was the most common, accounting for 61.54%. Regarding point mutation types, intermediate-risk was the most common, accounting for 62.50%, while intermediate-risk was prevalent in insertion mutation types, accounting for 75.00%. Notably, high risk was most common for mixed mutation types, accounting for 44.44%.

Table 3 shows that the 58 GIST patients were cross-classified based on two attributes of gene and cell types after which Fisher's exact probability test was performed. The chi-square value was 13.366. $P<0.05$ indicated a moderate correlation between gene and cell types.

Table 4 shows that 42 GIST patients were cross-classified based on two attributes of c-kit exon-11 mutations and tumor risk, and Fisher's exact probability test was performed. The chi-square value was 20.270. $P<0.05$ indicated a moderate correlation between c-kit exon-11 mutation type and tumor risk.

Discussion

The c-kit proto-oncogene is located on chromosome 4q12-13, and its expression product,

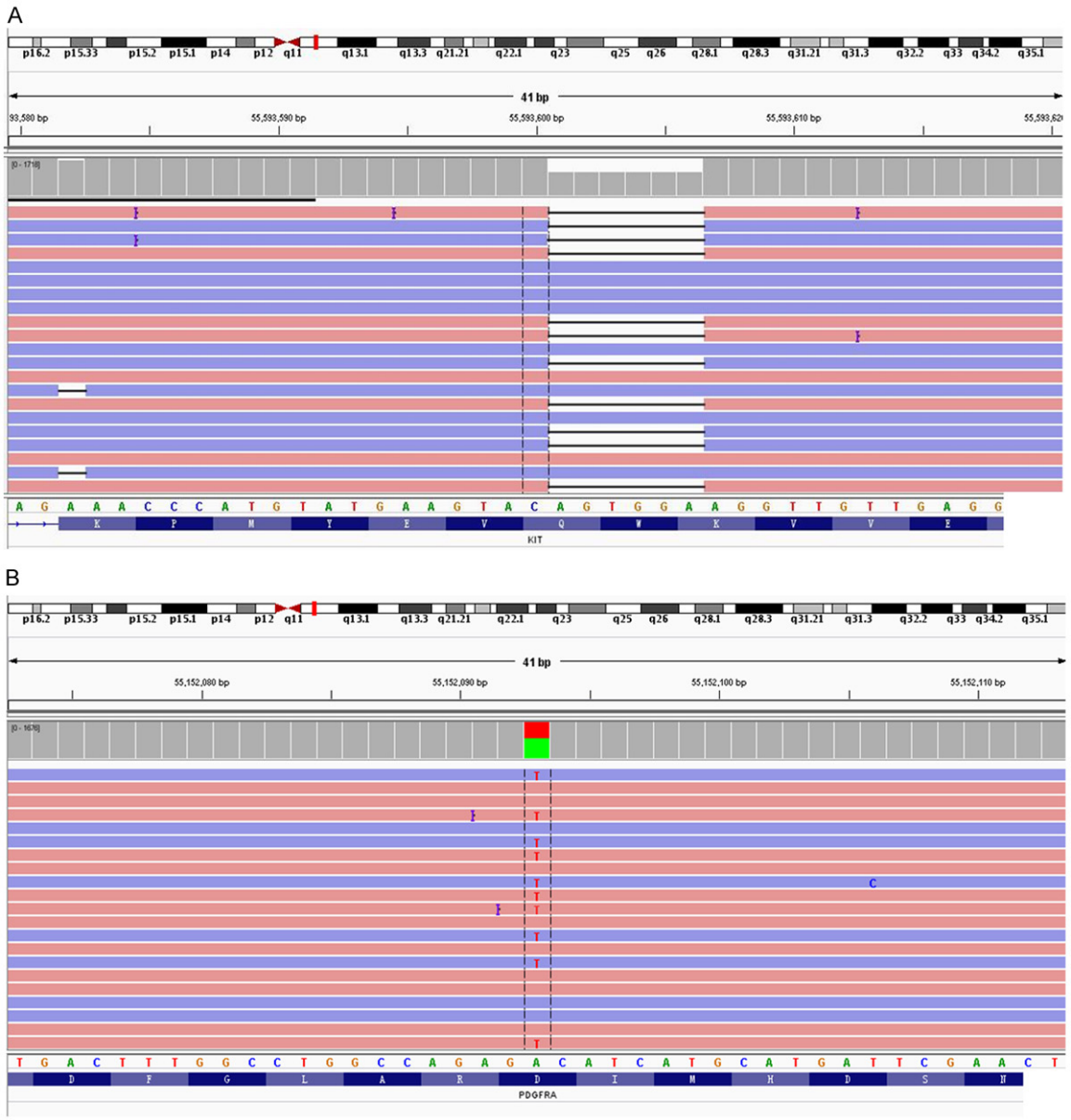

Figure 3. A. Mutations of c-kit exon-11 W557_K558del. B. Mutations of PDGFRα exon-18 D842V.

c-kit receptor, is the transmembrane glycoprotein type-III tyrosine kinase receptor (CD117). Under normal circumstances, the c-kit protein binds a ligand called stem cell factor (SCF) to form a dimer that activates transcription factors in the cytoplasm, thereby regulating gene expression and controlling cell proliferation and differentiation [9]. The PDGFRα gene is very similar to c-kit. It belongs to the type-III tyrosine-protein kinase family and encodes platelet-derived growth factor receptor-α. When PDGFRα binds its ligand, PDGF, it results in phosphorylation of tyrosine residues, which regulate cell growth, proliferation, differentiation, and apoptosis [10]. Mutations in the proximal regions of c-kit and PDGFRα genes can continuously activate proteins without ligand binding. This activates downstream signaling pathways, leading to the occurrence of GISTs. Therefore, the mutant, c-kit/PDGFRα, can be used as a diagnostic marker and a treatment target for GIST.

GIST is most prevalent in adults aged above 60-years with an incidence ratio of 1:1 for men and women [11]. Among the 58 GIST

Table 1. GIST genotype and clinico-pathologic features

	c-kit (51)	PDGFRα (5)	Wild type (2)	*P* values
Sex, n (%)				0.117
Male	23 (45.10)	4 (80.00)	2 (100.00)	
Female	28 (54.90)	1 (20.00)	0 (0.00)	
Age, n (%)				0.765
≤50	12 (23.53)	1 (20.00)	1 (50.00)	
>50	39 (76.47)	4 (80.00)	1 (50.00)	
Location, n (%)				0.619
Stomach	24 (47.06)	4 (80.00)	2 (100.00)	
Small intestine	16 (31.37)	0 (0.00)	0 (0.00)	
Colorectum	3 (5.88)	0 (0.00)	0 (0.00)	
Parenteral	8 (15.69)	1 (20.00)	0 (0.00)	
Cell type, n (%)				
Spindle	37 (72.55)	2 (40.00)	1 (50.00)	0.022
Epithelioid	2 (3.92)	0 (0.00)	1 (50.00)	
Mixed	1 (1.96)	2 (40.00)	0 (0.00)	
NA	11 (21.57)	1 (20.00)	0 (0.00)	
Mitotic count (/50HPF), n (%)				
≤5	30 (58.82)	4 (80.00)	1 (50.00)	1.000
>5	15 (29.41)	1 (20.00)	1 (50.00)	
NA	6 (11.76)	0 (0.00)	0 (0.00)	
Tumor diameter (cm), n (%)				
≤2	5 (9.80)	0 (0.00)	0 (0.00)	0.805
>2 to ≤5	16 (31.37)	2 (40.00)	1 (50.00)	
>5 to ≤10	21 (41.18)	2 (40.00)	0 (0.00)	
>10	7 (13.73)	1 (20.00)	1 (50.00)	
NA	2 (3.92)	0 (0.00)	0 (0.00)	
Risk, n (%)				0.580
Very low	3 (5.88)	0 (0.00)	0 (0.00)	
Low	6 (11.76)	2 (40.00)	1 (50.00)	
Intermediate	18 (35.29)	1 (20.00)	0 (0.00)	
High	20 (39.22)	2 (40.00)	1 (50.00)	
NA	4 (7.84)	0 (0.00)	0 (0.00)	
CD117, n (%)				1.000
+	49 (96.08)	5 (100.00)	2 (100.00)	
-	1 (1.96)	0 (0.00)	0 (0.00)	
NA	1 (1.96)	0 (0.00)	0 (0.00)	
DOG1, n (%)				1.000
+	49 (96.08)	5 (100.00)	2 (100.00)	
NA	2 (3.92)	0 (0.00)	0 (0.00)	
CD34, n (%)				0.288
+	48 (94.12)	4 (80.00)	2 (100.00)	
-	1 (1.96)	1 (20.00)	0 (0.00)	
NA	2 (3.92)	0 (0.00)	0 (0.00)	
Ki-67 (%), n (%)				1.000
≤5	24 (47.06)	3 (60.00)	1 (50.00)	
5-10	8 (15.69)	0 (0.00)	0 (0.00)	
≥10	19 (37.25)	2 (40.00)	1 (50.00)	
Metastasis, n (%)				1.000
+	4 (7.84)	0 (0.00)	0 (0.00)	
-	47 (92.16)	5 (100.00)	2 (100.00)	

Table 2. Forms of c-kit exon-11 mutations and clinico-pathologic characteristics

	Deletion (13)	Point mutation (16)	Insertion (4)	Mixed (9)	*P* values
Sex, n (%)					0.233
Male	8 (61.54)	4 (25.00)	2 (50.00)	3 (33.33)	
Female	5 (38.46)	12 (75.00)	2 (50.00)	6 (66.67)	
Age, n (%)					0.075
≤50	2 (15.38)	2 (12.50)	0 (0)	5 (55.56)	
>50	11 (84.62)	14 (87.50)	4 (100.00)	4 (44.44)	
Location, n (%)					0.250
Stomach	5 (38.46)	12 (75.00)	3 (75.00)	3 (33.33)	
Small intestine	4 (30.77)	2 (12.50)	0 (0.00)	4 (44.44)	
Colorectum	2 (15.38)	0 (0.00)	0 (0.00)	0 (0.00)	
Parenteral	2 (15.38)	2 (12.50)	1 (25.00)	2 (22.22)	
Cell type, n (%)					0.395
Spindle	7 (53.85)	12 (75.00)	2 (50.00)	8 (88.89)	
Epithelioid	2 (15.38)	0 (0.00)	0 (0.00)	0 (0.00)	
Mixed	1 (7.69)	0 (0.00)	0 (0.00)	0 (0.00)	
NA	3 (23.08)	4 (25.00)	2 (50.00)	1 (11.11)	
Mitotic count (/50HPF), n (%)					0.408
≤5	6 (46.15)	12 (75.00)	3 (75.00)	4 (44.44)	
>5	6 (46.15)	2 (12.50)	1 (25.00)	3 (33.33)	
NA	1 (7.69)	2 (12.50)	0 (0.00)	2 (22.22)	
Tumor diameter (cm), n (%)					0.120
≤2	1 (7.69)	1 (6.25)	1 (25.00)	1 (11.11)	
>2 to ≤5	5 (38.46)	3 (18.75)	0 (0.00)	5 (55.56)	
>5 to ≤10	4 (30.77)	10 (62.50)	3 (75.00)	2 (22.22)	
>10	3 (23.08)	0 (0.00)	0 (0.00)	1 (11.11)	
NA	0 (0.00)	2 (12.50)	0 (0.00)	0 (0.00)	
Risk, n (%)					0.039
Very low	1 (7.69)	1 (6.25)	0 (0.00)	1 (11.11)	
Low	1 (7.69)	2 (12.50)	0 (0.00)	2 (22.22)	
Intermediate	2 (15.38)	10 (62.50)	3 (75.00)	1 (11.11)	
High	8 (61.54)	1 (6.25)	1 (25.00)	4 (44.44)	
NA	1 (7.69)	2 (12.50)	0 (0.00)	1 (11.11)	
CD117, n (%)					0.528
+	13 (100.00)	15 (93.75)	4 (100.00)	8 (88.89)	
-	0 (0.00)	0 (0.00)	0 (0.00)	1 (11.11)	
NA	0 (0.00)	1 (6.25)	0 (0.00)	0 (0.00)	
DOG1, n (%)					1.000
+	12 (92.31)	15 (93.75)	4 (100.00)	9 (100.00)	
NA	1 (7.69)	1 (6.25)	0 (0.00)	0 (0.00)	
CD34, n (%)					1.000
+	13 (100.00)	15 (93.75)	4 (100.00)	9 (100.00)	
NA	0 (0.00)	1 (6.25)	0 (0.00)	0 (0.00)	
Ki-67, n (%)					0.212
≤5	5 (38..46)	10 (62.50)	3 (75.00)	3 (33.33)	
5-10	1 (7.69)	3 (18.75)	1 (25.00)	1 (11.11)	
≥10	7 (53.85)	3 (18.75)	0 (0.00)	5 (55.56)	
Metastasis, n (%)					0.174
+	1 (7.69)	0 (0.00)	0 (0.00)	2 (22.22)	
-	12 (92.31)	16 (100.00)	4 (100.00)	7 (77.78)	

Table 3. Cross classification table of the 58 GIST patients by gene type and cell type

Cell type	Genetic type			Total
	c-kit	PDGFRα	Wild-type	
Spindle	37	2	1	40
Epithelioid	2	0	1	3
Mixed	1	2	0	3
NA	11	1	0	12
Total	51	5	2	58

Table 4. Cross-classification table of 42 GIST patients by c-kit exon-11 mutation forms and tumor risk

Risk	c-kit exon-11 mutant form				Total
	Deletion	Point mutation	Insertion	Mixed	
Very low	1	1	0	1	3
Low	1	2	0	2	5
Intermediate	2	10	3	1	16
High	8	1	1	4	14
NA	1	2	0	1	4
Total	13	16	4	9	42

patients in this study, 29 were male while the rest were female (1:1), with a median age of 57.5-years. The most common anatomic location for GIST was the stomach (55.6%), followed by the small intestine (31.8%), colon (6.0%), esophagus (0.7%), and other body parts (5.5%) [11]. 30 cases (51.7%) had tumors with a stomach origin, 16 cases (27.6%) in the small intestine, 3 cases (5.2%) in the colorectum, and 9 cases (15.5%) outside the gastrointestinal tract (including the abdomen, pelvic, and peritoneal cavities).

The spindle cell type was the most common for the c-kit gene, accounting for 72.55%. On the other hand, the spindle and mixed spindle-epithelioid cell types were prevalent for the PDGFRα gene, accounting for 40%. Moreover, the spindle and epithelioid cell types were the most common in the WT genotype, accounting for 50%. Differences between cell types in different gene types were significant (P = 0.022), with a moderate correlation. It has been reported that, histologically, PDGFRα mutant GIST usually presents with epithelioid or mixed spindle-epithelioid cell type appearances [12], which contrasts with our findings. These differences could be due to the small number of samples included in this study, or to the fact that PDGFRα gene mutations in this study were all exon-18 mutations, whereas those in the previous reported study were exon-14 mutations. C-kit exon-11 point mutations are characterized by low mitotic numbers with an average tumor size of <5 cm. Moreover, 5-year recurrence-free survival (RFS) (50.7%) of c-kit exon-11 point mutations is higher than those of deletion mutations (28.1%) and repeat mutations (40%). Consistently, we show that point mutations have an intermediate risk, whereas deletion mutations have a high risk.

In this study, the positive rates for CD117, DOG-1, and CD34 were 96.6%, 96.6%, and 93.1%, respectively, consistent with total mutation rates of c-kit and PDGFRα (96.6%). It has been reported that the positive rate of CD117 is independent of mutation status of c-kit and PDGFRα [13]. Ki-67 has been considered to be a marker of proliferative cell activity [14]. In this study, the relationship between Ki-67 index and gene status was not significant.

Moreover, the total mutation rate of c-kit and PDGFRα was 96.6%, consistent with a study performed in Panama (94.9%) [15], but higher than the rates in other reports [16, 17]. The mutation frequency of c-kit exon-11 was 82.4%, which contrasts with previously reported rates. These discrepancies may be attributed to application of different genetic testing methods and use of varying sample sizes across studies. We found 13 cases with c-kit gene exon-11 deletion mutations, among whom 6 cases were W557_K558del (2 cases with high risk and 2 cases with intermediate risk). Some studies have suggested that GIST, with 557-558 codon deletion mutation is more aggressive and easily undergoes metastasis, thus has poor prognostic outcomes [18]. Joensuu et al. [19] classified them according to the number of missing codons, and believed that the RFS for deletion mutation of the large fragment of c-kit exon-11 was shorter than the mutation with only one codon missing. There were 2 cases with one codon missing (2 high-risk cases) and 11 cases with ≥2 codons missing (6 high-risk cases). It has been reported [20] that mutations in exon-9 of the c-kit gene tend to occur in the small intestine, with a higher malignant potential.

There were 7 cases of exon-9 mutations in the study, 5 cases in the small intestine, and 2 cases in the stomach and esophagus. 4 of the 7 cases were high risk. 3 were in the small intestine, and one was in the stomach, consistent with findings from previous studies.

In summary, the c-kit gene mutant type had more spindle-shaped cell types than epithelioid and mixed spindle-epithelioid cell types. Among the PDGFRα gene mutations, spindle and mixed spindle-epithelioid cell types were the most prevalent. In the WT genotype, spindle and epithelioid cell types were the most common. For c-kit exon-11 mutant forms, deletion mutations and mixed mutations had higher risk, while point and insertion mutations had intermediate-risk. Future, large-scale clinical and basic research studies should aim at investigating the importance of gene mutations in GIST.

Acknowledgements

Written informed consent for publication was obtained from all participants.

Disclosure of conflict of interest

None.

Abbreviations

GIST, Gastrointestinal Stromal Tumors; c-kit, c-kitproto-oncogeneprotein; PDGFRα, Platelet-derived Growth Factor Receptor; PCR, Polymerase Chain Reaction; NGS, Next Generation Sequencing; NIH, National Institutes of Health; WT, Wild Type; HPF, High Power Field; SCF, Stem Cell Factor; RFS, Recurrence-free Survival.

Address correspondence to: Dr. Su-Sheng Shi, Department of Pathology, Cancer Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, No. 17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China. Tel: +86-10-87788548; E-mail: drshisusheng@163.com

References

[1] Villanueva MT. Ripretinib turns off the switch in GIST. Nat Rev Cancer 2019; 19: 370.

[2] Belinsky MG, Rink L, Flieder DB, Jahromi MS, Schiffman JD, Godwin AK and Mehren M. Overexpression of insulin-like growth factor 1 receptor and frequent mutational inactivation of SDHA in wild-type SDHB-negative gastrointestinal stromal tumors. Genes Chromosomes Cancer 2013; 52: 214-224.

[3] Vitiello GA, Bowler TG, Liu M, Medina BD, Zhang JQ, Param NJ, Loo JK, Goldfeder RL, Chibon F, Rossi F, Zeng S and DeMatteo RP. Differential immune profiles distinguish the mutational subtypes of gastrointestinal stromal tumor. J Clin Invest 2019; 129: 1863-1877.

[4] Oppelt PJ, Hirbe AC and Van Tine BA. Gastrointestinal stromal tumors (GISTs): point mutations matter in management, a review. J Gastrointest Oncol 2017; 8: 466-473.

[5] Lasota J, vel Dobosz AJ, Wasag B, Wozniak A, Kraszewska E, Michej W, Ptaszynski K, Rutkowski P, Sarlomo-Rikala M, Steigen SE, Schneider-Stock R, Stachura J, Chosia M, Ogun G, Ruka W, Siedlecki JA and Miettinen M. Presence of homozygous KIT exon 11 mutations is strongly associated with malignant clinical behavior in gastrointestinal stromal tumors. Lab Invest 2007; 87: 1029-1041.

[6] Lasota J, Dansonka-Mieszkowska A, Sobin LH and Miettinen M. A great majority of GISTs with PDGFRA mutations represent gastric tumors of low or no malignant potential. Lab Invest 2004; 84: 874-883.

[7] Corless CL, Schroeder A, Griffith D, Town A, McGreevey L, Harrell P, Shiraga S, Bainbridge T, Morich J and Heinrich MC. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 2005; 23: 5357-5364.

[8] Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008; 39: 1411-1419.

[9] Bettegazzi C and Erra S. Gastrointestinal stromal tumors: a rare nosological entity and a model example for the use of personalized therapy with a molecular basis. Recenti Prog Med 2015; 106: 52-57.

[10] Taylor ML and Metcalfe DD. Kit signal transduction. Hematol Oncol Clin North Am 2000; 14: 517-535.

[11] Søreide K, Sandvik OM, Søreide JA, Giljaca V, Jureckova A and Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. Cancer Epidemiol 2016; 40: 39-46.

[12] Barnett CM, Corless CL and Heinrich MC. Gastrointestinal stromal tumors: molecular markers and genetic subtypes. Hematol Oncol Clin North Am 2013; 27: 871-888.

[13] Lasota J and Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. Histopathology 2008; 53: 245-266.

[14] Hasegawa T, Matsuno Y, Shimoda T and Hirohashi S. Gastrointestinal stromal tumor: consistent CD117 immunostaining for diagnosis, and prognostic classification based on tumor size and MIB-1 grade. Hum Pathol 2002; 33: 669-676.

[15] Mendoza Y, Singh C, Castillo Mewa J, Fonseca E, Smith R and Pascale JM. Beginning of personalized medicine in Panama: Molecular and pathological characteristics of gastrointestinal stromal tumors from archival paraffin-embedded tissue. Oncol Lett 2011; 2: 941-947.

[16] Guenat D, Deroo O, Magnin S, Chaigneau L, Monnien F, Borg C, Mougin C, Emile JF and Pretet JL. Somatic mutational spectrum analysis in a prospective series of 104 gastrointestinal stromal tumors. Oncol Rep 2017; 37: 1671-1681.

[17] Braggio E, Braggio DDA, Small IA, Lopes LF, Valadao M, Gouveia ME, Moreira ADS, Linhares E, Romano S, Bacchi CE, Renault IZ, Guimaraes DP and Ferreira CG. Prognostic relevance of KIT and PDGFRA mutations in gastrointestinal stromal tumors. Anticancer Res 2010; 30: 2407-2414.

[18] Martín J, Poveda A, Llombart-Bosch A, Ramos R, López-Guerrero JA, García del Muro J, Maurel J, Calabuig S, Gutierrez A, González de Sande JL, Martínez J, De Juan A, Laínez N, Losa F, Alija V, Escudero P, Casado A, García P, García P, Blanco R and Buesa JM. Deletions affecting codons 557-558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS). J Clin Oncol 2005; 23: 6190-6198.

[19] Joensuu H, Rutkowski P, Nishida T, Steigen SE, Brabec P, Plank L, Nilsson B, Braconi C, Bordoni A, Magnusson MK, Sufliarsky J, Federico M, Jonasson JG, Hostein I, Bringuier PP and Emile JF. KIT and PDGFRA mutations and the risk of GI stromal tumor recurrence. J Clin Oncol 2015; 33: 634-642.

[20] Martín-Broto J, Rubio L, Alemany R and López-Guerrero JA. Clinical implications of KIT and PDGFRA genotyping in GIST. Clin Transl Oncol 2010; 12: 670-676.