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KIT/PDGFRA mutations and their associations with clinicopathological parameters in gastrointestinal stromal tumors of Vietnamese patients

Linh Dieu Vuong[1], Quang Ngoc Nguyen[1,*]

[1]Pathology and Molecular Biology Center, National Cancer Hospital K, 30 Cau Buou Street, Thanh Tri, Hanoi, Vietnam
[*]Corresponding author: quangnguyen@bvk.org.vn

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Abstract

The study was designed to evaluate the prevalence of *KIT*/*PDGFRA* alterations, and to analyze the relationship between gene changes and clinical/pathological characteristics of Vietnamese GIST patients. Cross-sectional research was performed on 177 cases with GIST tumor, which was diagnosed in K Hospital, Vietnam. Realtime PCR allows identifying *KIT*/*PDGFRA* mutations. The frequency of *KIT* and *PDGFRA* mutations were 60.5% and 13.6%, in turn. In GISTs, KIT and PDGFRA modifications were not co-existence. *KIT*, as well as *KIT/PDGFRA*, changes tend to be in smaller tumor sizes (p<0.05). Moreover, *KIT* mutations had more significant frequency in the stomach than in other sites (intestinal and outside the gastrointestinal tract). *PDGFRA* alterations tend to be common in low-risk classification (p=0.032). The results provide molecular profiling, including *KIT* and *PDGFRA* mutations, which orient targeted therapy for Vietnamese GISTs, in which *KIT* exon 11 mutations are the most sensitive to imatinib, in contrast, the *PDGFRA* exon 18 variants (D842V) are resistant to this TKI. Additionally, GIST patients carrying *PDGFRA* mutation can be a potential biomarker for predicting the risk of tumor classification in the Vietnamese population.

Keywords: Clinicopathological characteristics, Gastrointestinal stromal tumors (GIST), *KIT/PDGFRA*, Targeted therapy

1. Introduction

In gastrointestinal machinery, gastrointestinal stromal tumors (GISTs) have the major rates of primary malignancies. The most origin of tumor position is the stomach (60-70%). The intestine and the outside gastrointestinal tract have lower prevalence. Immunohistochemistry tests of molecular biomarkers, such as CD117, CD34, smooth muscle actin, and S100 are common diagnoses GISTs [1, 2]. The entire surgical excision is the usual treatment of localized GISTs despite a high relapse. Thus, modern medicine requires essential biomarkers that are able to predict the GISTs' recurrence, including Ki67, PCNA expression, and DNA flow cytometry [3, 4].

With GIST patients, deletions in *KIT* gene account for around 75-80%, followed by insertions, substitutions or multiple mutations. Other mutations occur rarely, such as *KIT* alterations in exons 8, 9, 13, 17 and *PDGFRA* mutations (platelet-derived growth factor receptor) [5, 6]. So, around 10-15% of GISTs do not have *KIT* or *PDGFRA* changes, which are not able to activate mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) signaling pathways. Alongside the identification of modifications linked with these tumors, the treatment has evolved extremely [5, 7].

Imatinib, *KIT* and *PDGFRA* inhibitors have efficacy for metastatic GISTs treatment. There are two types of *KIT*/*PDGFRA* mutations, including primary and secondary alterations [8, 9]. They play certain roles in GISTs pathogenesis and drug resistance, respectively [10, 11]. Data from experiments as well as clinical trials recommend that *KIT* and/or *PDGFRA* mutations may perhaps influence imatinib sensitivity, as a consequence should be considered surrounded by therapeutic strategies. The outstanding characteristic of GISTs-targeted

therapy is to reduce the risk of relapse and improve the duration and quality of life for patients. Even though these genetic changes stimulate tumorigenesis, they not only predict response to targeted therapies but also contribute prognostic information.

Alteration of tyrosine kinase receptors (RTKs) can be led to drug resistance that is capable of appearing at any time during the targeted treatment. Furthermore, genetic characteristics are able to predict the response to therapy with TKIs, nevertheless, mutation status serving as a prognostic element holds on debatable. Many studies about *KIT*/*PDGFRA* mutations have been performed worldwide; however, there is a lack of validation and evidence of its role in Vietnamese patients suffering from GISTs. This research will be a basic step that consists of detecting the frequency of genetic variations in *KIT* and *PDGFRA* and evaluating the correlation of each mutation with the clinicopathological parameters of the Vietnamese GISTs.

2. Materials and methods

2.1 Tissue block of GIST patients

From Aug 2017 and Aug 2022, at the Vietnamese National Cancer Hospital, the study was conducted on 177 formalin-fixed paraffin-embedded (FFPE) blocks with GISTs by the cross-sectional descriptive method. Criteria for specimens included diagnosed histologically GIST according to the American Joint Committee on Cancer and CD117 expression. The study was carried out in accordance with the Helsinki Declaration Principles. The research followed the ethics committee (02-2022/NCHG-HDDD) and had the informed consent form.

2.2 Isolation of DNA from GIST blocks

Cobas® DNA Sample Preparation Kit (Roche, Branchburg, NJ 08876, USA) was used for total DNA isolation from FFPE blocks of GIST patients. Then, genomic DNA will be quantified by Qubit dsDNA BR Assay Kits, as well as, electrophoresis on 0.5% agarose gel in order to evaluate DNA integrity.

2.3 Investigation KIT, PDGFRA genetic alterations from GIST blocks

KIT and *PDGFRA* somatic mutations were detected by GIST Mutation Detection Kit v1.7 (EntroGen, CA 91367, USA). The whole protocol was certain to follow the instructions in this manual using supported instruments and validated reagents.

2.4 Statistical analyzation

The research focuses on the frequency of *KIT* and *PDGFRA* variants and the correlation between genetic abnormalities and characteristics of Vietnamese GISTs, based on SPSS software version 20.0. For all statistical analyses, a $p < 0.05$ was considered significant.

3. Results

3.1. Clinicopathological parameters of GIST patients

The clinicopathological particularities of 177 GIST patients were exhibited in Table 1. GISTs' age was diagnosed from 16 to 85 years (55.8 ± 13.4). The proportion of male patients is approximately equal to females, reaching 1.08. Tumors smaller than 5 cm and larger than 10 cm were predominant, up to over 70%. One hundred seventy-seven patients with GIST including 103 (58.2%), 53 (29.9%) and 21 (11.9%) were collected from the stomach, intestinal and outside the gastrointestinal tract (esophagus, mesentery, peritoneum…), respectively. Based on risk classification, there were 75 (42.4%) low-risk, 19 (10.7%) moderate-risk and 83 (46.9%) high-risk. On the other hand, 118 (66.7%), 27 (15.2%) and 32 (18.1%) patients have <5/50 high-power fields (HPF), 6-10/50 HPF and >10/50 HPF, respectively, characterized by the mitotic index.

Table 1 Clinicopathological parameters of GIST patients.

Characteristics	N	%
	177	100
Age		
> 55.8	98	55.4
< 55.8	79	44.6
Gender		
Male	92	52.0
Female	85	48.0
Tumor Size (cm)		
< 5	61	34.5
5-10	44	24.8
> 10	72	40.7
Tumor Position		
Stomach	103	58.2
Intestinal	53	29.9
Outside the gastrointestinal tract	21	11.9
Risk Classification		
Low	75	42.4
Moderate	19	10.7
High	83	46.9
Mitotic Index		
<5/50	118	66.7
6-10/50	27	15.2
>10/50	32	18.1

3.2. The frequency of KIT and PDGFRA changes and their associations with characteristics of GISTs

Genetic abnormalities in 177 participants were detailed in Table 2. KIT gene mutation was identified in 107/177 cases, reaching 60.5%. Specifically, there are 97/107 (90.7%) and 10/107(9.3%) patients who carried alterations in exon 11 and exon 9, in turn. 97 alterations coming out of exon 11, deletions had a greater part of changes, achieving 70.1%, including EX11_p.W557_E561del and EX11_p.W557_K558del variants. There are 29 patients who carried a *KIT* missense mutation at codons 559, 560, and 576 from exon 11 (EX11_p.L576P, EX11_p.V559A, EX11_p.V559G, EX11_p.V560D variants). All mutations detected in exon 9 of the *KIT* gene are EX9_p.Y503_F504insAY mutation (10/10). *PDGFRA* mutation occurred in 13.6% (24/177) of cases in codon 842 (EX18_p.D842V) of the exon 18. The mutation of either *KIT* or *PDGFRA* was detected in 74.0% (131/177) of the cases examined. There was no meaningful interaction between *KIT* and *PDGFRA* variations with age, sexual characteristics and mitotic index. The research indicated a critical correlation inward of *KIT* or *KIT*/*PDGFRA* modifications with tumor size (p<0.0001). *KIT* mutations tended to exist in the stomach, while *PDGFRA* modifications had a higher incidence in the low-risk tumors (p<0.05). Evaluating the correlation between *KIT* and *PDGFRA* somatic variants in 177 GISTs, the results demonstrated that these mutations are mutually exclusive in the Vietnamese GISTs (p<0 .0001).

Table 2 Association between *KIT/PDGFRA* abnormalities and characteristics of GIST patients.

		KIT Mutation		*p-value*	*PDGFRA* mutation		*p-value*	*KIT/PDGFRA* mutation		*p-value*
N		Yes	%		Yes	%		Yes	%	
	177	107	60.5		24	13.6		131	74.0	
Age				*0.105*			*0.101*			*0.598*
> 55.8	98	54	55.1		17	17.3		71	72.4	
< 55.8	79	53	67.1		7	8.9		60	63.3	
Gender				*0.266*			*0.817*			*0.289*
Male	92	52	56.5		13	14.1		65	70.7	
Female	85	55	64.7		11	12.9		66	77.6	
Tumor Size (cm)				*<0.0001*			*0.193*			*<0.0001*
< 5	61	48	78.7		5	8.2		53	86.9	
5-10	44	27	61.4		9	20.5		36	81.8	
> 10	72	32	44.4		10	13.9		42	58.3	
Tumor Position				*<0.0001*			*0.156*			*<0.0001*
Stomach	103	83	80.6		10	9.7		93	90.3	
Intestinal	53	20	37.7		9	17.0		29	54.7	
Outside the gastrointestinal tract	21	4	19.0		5	23.8		9	42.9	
Risk Classification				*0.096*			*0.032*			*0.068*
Low	75	43	57.3		16	21.3		59	78.7	
Moderate	19	8	42.1		2	10.5		10	52.6	
High	83	56	67.5		6	7.2		62	74.7	
Mitotic Index				*0.087*			*0.066*			*0.747*
<5/50	118	78	66.1		11	9.3		89	75.4	
6-10/50	27	14	51.9		6	22.2		20	74.1	
>10/50	32	15	46.9		7	21.9		22	68.8	

χ^2 test (excluding Fisher's extract test for values smaller than five)

4. Discussions

Activating mutations that occur at exons 9, 11, 13, or 17 of *KIT* or exons 12, 14, or 18 of *PDGFRA*, is the most usual molecular event of GISTs [12]. Wild-type GISTs (lacking *KIT* and/or *PDGFRA* alterations) may perhaps have other somatic mutations, approximately 10-15%. Each type of mutation will have a different response mechanism to tyrosine kinase inhibitor (TKI), in which, *KIT* exon 11 mutations are the most sensitive to imatinib, in contrast, the *PDGFRA* exon 18 variants (D842V) are resistant to this TKI [13-14].

Located on the long arm of the fourth human chromosome, The *KIT* proto-oncogene consists of 21 exons. *KIT* mutations activate several signaling pathways, leading to uncontrolled cell proliferation and tumorigenesis [15]. The *KIT* mutation rate varies among countries (21-92%), the results indicated that the frequency of *KIT* changes in Vietnamese GISTs was 60.5%, consistent with other publications [2, 16-19]. The reasons for the variance might be concerned with ethnicity-dependent alteration levels, the experimental methods and the characteristics of specimens. *KIT* alterations and several factors, such as age, gender, risk classification and mitotic index are random, in contrast, tumor size, as well as, position and this mutation exhibited statistically significant differences (p>0.05). Up to now, numerous reports have been made to demonstrate that primary *KIT* variants in exon 11,

which tend to occur in the stomach, are consistent with Vietnamese GISTs [20, 21]. Moreover, 10/107 cases (9.3%) harbored mutations in exon 9 of *KIT*. This rate was a higher level, which was reported by Lasota et al. (6/200, 3.0%), but consistent with exon 9 *KIT* mutation rate varies among publications (7.2-10.9%) [16, 19, 20]. The research did not reveal alterations in exons 13 and 17 of *KIT*, similar to the reports that these are rare mutations. Most importantly, the *KIT* mutation rate was significantly higher in the stomach (reaching over 80%), compared to other sites of tumor, consistent with the report of Baskin Y et al. (2016) [22].

Similar to the *KIT* gene, the *PDGFRA* gene is also located on the fourth chromosome, containing 23 exons [23]. *PDGFRA* variations may play a certain role in GISTs' tumorigenesis and are common in patients that do not carry *KIT* mutations. The rate of *PDGFRA* mutation varies among reports (5.4-20.0%) [22]. As a prognosis biomarker, *PDGFRA* alteration has been widely utilized in the predictive metastasis GISTs. For instance, patients who harbored exon 18 *PDGFRA* mutation tend to be at lower risk of metastasis than others who carried *KIT* change. In this study, the *PDGFRA* gene is mutated in 13.6% (24/177), and particularly, alterations in the *KIT* and *PDGFRA* genes are mutually exclusive (p<0.05). All *PDGFRA* variants (100%, 24/24) which were identified in Vietnamese GISTs, were D842V substitution (aspartic acid (D) to valine (V)), slightly different from reports of Rizzo A et al. (2021) and Debiec-Rychter M et al. (2004) [24, 25]. *PDGFRA* mutation was significantly associated with low-risk classification (p=0.032), which was different from the previous report, which showed that *PDGFRA* mutated cases tended to occur randomly with risk classification of the tumors [22]. This result suggested that GIST patients carrying *PDGFRA* mutation can be a potential biomarker for the prediction tumor of risk classification in the Vietnamese population.

At present, the Food and Drug Administration (FDA) approved Imatinib (a selective inhibition on *PDGFRA* and *KIT*) in clinical use [6-8]. Besides being sensitive mutations in exon 11 of the *KIT* gene, *KIT* exon 9 mutants are slightly worse, and particularly, changes in the other exons of *KIT* and D842V variants are even resistant to Imatinib in the GISTs treatment [26-28]. In contrast, numerous studies have been made to indicate that GIST patients who carry other mutations in exon 18 of the *PDGFRA* gene or do not express CD117 protein may respond to this targeted therapy [29].

Currently, *KIT* and *PDGFRA* mutations have been more widely used in the prognosis, treatment, recurrence and monitoring of the resistance of GISTs worldwide. Many studies on *KIT*/*PDGFRA* markers have been conducted; however, there is a lack of data on their utility in Vietnamese patients suffering from GISTs. A comprehensive evaluation of *KIT/PDGFRA* mutations in Vietnamese GISTs will lay the foundation to empower precision cancer medicine.

5. Conclusions

The frequency of *KIT* and *PDGFRA* mutations were 60.5% and 13.6%, respectively. *KIT*, as well as *KIT/PDGFRA*, changes tend to be in smaller tumor sizes (p<0.05). Moreover, *KIT* mutations had more significant frequency in the stomach than in other sites. *PDGFRA* alterations tend to be common in low-risk classification. In GISTs, KIT and PDGFRA modifications were not co-existence. The results provide the status of *KIT* and *PDGFRA* mutations, which orient targeted therapy for Vietnamese GISTs.

6. Author Contributions

Linh D. Vuong: Data curation, Formal analysis, Methodology, Resources, Software, Validation Visualization Writing – original draft. Quang N. Nguyen: Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Writing – review & editing.

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