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An Unusual PDGFRA Mutation in Gastrointestinal Stromal Tumor and Its NGS Data Analysis

Dahui Qin, MD and PhD*

Department of Pathology, Moffitt Cancer Center, United Sates

***Corresponding Author:**
Dahui Qin, Department of Pathology, Moffitt Cancer Center, United Sates

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1. Abstract

1.1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract [1]. About 75% of GISTs harbor activating mutations of KIT and About 10% of GISTs harbor PDGFRA activating mutations [2]. PDGFRA is the second most mutated oncogene in GIST and are particularly associated with gastric tumors [3,4]. The introduction of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of GISTs, with specific efficacy seen in tumors with PDGFRA and KIT mutations. However, different PDGFRA mutations can impact the response to these therapies differently [5,6]. For example, the PDGFRA D842V mutation is resistant to imatinib but may respond to newer drugs like avapritinib. Therefore, it is critically important to identify any specific PDGFRA mutations in tumor molecular testing. Here, we report a case with an unusual PDGFRA mutation with a discussion about its NGS data analysis.

2. Case Description

A gentleman in his early 50s presented with a history of anemia. The work-up for anemia and GI bleeding found to have varices on endoscopy along with an anterior gastric lesion on the inferior aspect of the greater curvature of the stomach. Lesion was biopsied and was consistent with gastrointestinal stromal tumor. A wedge gastrectomy was performed. The tumor is solid subserosal/intramural mass, measuring 4.5 x 4 x3.5 cm and again diagnosedas GIST, spindle cell type, low grade, all margins being negative for GIST.The tumor tissue was submitted for molecular test. DNA was extracted from FFPE tumor tissue, using QIAGEN AllPrep DNA/RNA FFPE kit. Illumina TSO500 Next Generation Sequencing (NGS) panel was used for sequencing analysis.Molecular Findings: NGS test on DNA reported two PDGFRA mutations: PDGFRA, p.D842*, c.2524_2534del11, 21.1% and PDGFRA, p.D846Vfs*14, c.2537delA, 21.8%. On IGV view, these two mutations are adjacent to each other and are in cis (Figure 1, panel A). The RNA sequencing data indicated that the mutant was expressed (Figure 1, panel B) with the depth of reads of 1674 and 1620.

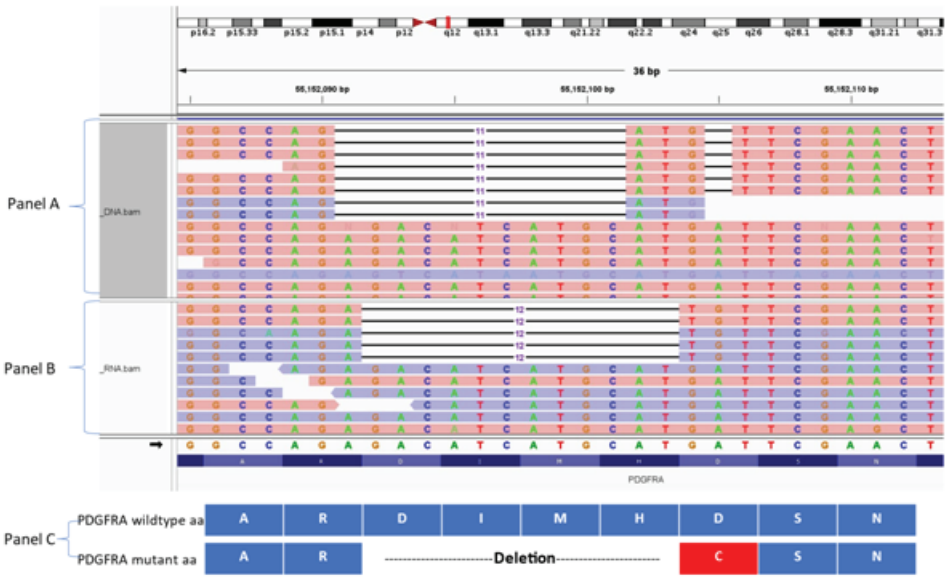

Figure 1. IGV view of an unusual PDGFRA mutation. Panel A shows DNA sequencing result. The software considers the first mutation is an 11 base pair (bp) deletion. Three bp away downstream, the software considers the nucleotide change is the second mutation with 1bp deletion. Panel B shows RNA sequencing result. The software for RNA analysis correctly called the mutation as one complex mutation, resulting a 12bp deletion. After such deletion, at the position of codon 842, the nucleotide sequence is TGT, which is translated into a cysteine (equivalent of D842C). Panel C is a schematic representation of a segment of wildtype PDGFRA amino acid sequence and a segment of mutant amino acid sequence. The red box represents codon 842.

3. Discussion

PDGFRA mutation is one of the driver mutations for GIST. It is more commonly seen in the GIST of stomach [2]. Patients with PDGFRA-mutant tumors have a lower risk of metastasis than patients with KIT-mutant tumors [7]. Binding of ligand to the extracellular domain of PDGFRA causes dimerization of PDGFRA and followed by autophosphorylation of the receptor and activation of downstream pathways such as RAS-MAPK, PI3K and PLC-γ that are involved in developmental and cellular responses. The most common PDGFRA mutations are p.D842V, which is an activating mutation resulting in constitutively activation of downstream signal transduction pathways. Tyrosine kinase inhibitors have been used in GIST treatment. Different PDGFRA mutations can impact the response to these therapies differently [5,6]. For example, the PDGFRA D842V mutation is resistant to imatinib but may respond to newer inhibitors [8-10]. Therefore, it is critically important to identify any specific PDGFRA mutations in tumor molecular testing. For this reported case, the NGS pipeline reported two PDGFRA mutations (Figure 1, panel A). One of them is a 11bp deletion, result in PDGFRA, p.D [9]842*, c.2524_2534del11. The other mutation is describe as a 1bp deletion, resulting in PDGFRA, p.D846Vfs*14, c.2537delA. Both mutations result in a stop codon. Generally speaking, the mutations with stop codon usually result in truncated proteins and lead to gene product inactivation, which is contradict to the pathogenesis of PDGFRA in GIST. Upon close looking at the sequencing data on IGV view, it was realized that the two mutations of this case were in cis and were in the vicinity of each other. Therefore, the nucleotide changes of these two mutations should be considered as one complex mutation rather than two independent mutations.The combination of these nucleotide changes generates a mutant DNA sequence as following: 5'CAACGTCCTCCTGGCACAAGGAAAAATTGTGAAGATCTGTGACTTTGGCCTGGCCAGA (codon842) TGTTCGAACTATGTGTCGAAAGGCAGTGTACGTCCTCACTTCCCTCACTGGTCAGGCTCATCCTCCTTCACTTTAATCTCTAAAGTCAGGTGTT3'. The actual PDGFRA coding sequence change is a 12-nucleotide in frame deletion followed by a D846C mutation. The RNA sequencing data indicated that this coding sequence change had been transcribed into RNA (Figure 1 panel B). It is conceivable that such mutated RNA could be translated into a protein (Figure 1 panel C).Such mutation is rare. Searching PubMed did not find any result. However, there are two similar PDGFRA mutation cases were identified [11,12]. Instead of a p.Asp842_Asp846delinsCys mutation, one case had p.Asp842_Asp846delinsGlu and the other case had p.Asp842_Asp846delinsGly mutation. Both cases were reported to be resistant to imatinib. The common features of these mutant is the deletion of four amino acid starting from PDGFRA codon 842 and followed by a missense mutation. This missense mutated amino acid is theoretically located at codon 846. However, in the presence of the four amino acid deletion, this missense mutation is actually equivalent to PDGFRA codon 842. This might offer an explanation why such mutations have imatinib resistant. Interestingly, a similar PDGFRA mutant has also been reported. It has the same four amino acid deletion, but not followed by the missense mutation. It is PDGFRA Asp842_845Hisdel. Such a mutation is also rare and has been reported as less than 1% of PDGFRA mutants [13]. There have been only a few cases reported [13-18]. However, he reported results both in vitro and in vivo indicates that such PDGFRA mutation is sensitive to imatinib [16-18]. This difference indicates that the missense mutation at PDGFRA codon 846 (equivalent to codon 842 after the deletion of four amino acid upstream) is critical for imatinib resistance as observed in PDGFRA D842V mutant.

4. Conclusion

PDGFRA mutations account for about 10% GIST pathogenesis. Different PDGFRA mutations lead to different responses to different tyrosine kinase inhibitors. NGS is a powerful method in detecting PDGFRA mutations. However, different NGS assays may use different software in data analysis. The output of results may not always reflect the real changes in DNA sequence. A close look at the NGS sequencing data on IGV may be necessary in NGS data analysis and reporting the NGS result..

References

1. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol. 2004;22(18):3813-25.
2. Arends MJ, Fukayama, Masashi, Klimstra, David S. etc. Digestive system tumours. Board WCoTE, editor. Lyon (France): International Agency for Research on Cancer. 2019.
3. Cassier PA, Ducimetiere F, Lurkin A, Ranchere-Vince D, Scoazec JY, Bringuier PP, et al. A prospective epidemiological study of new incident GISTs during two consecutive years in Rhone Alpes region: incidence and molecular distribution of GIST in a European region. Br J Cancer. 2010;103(2):165-70.
4. Blay JY, Kang YK, Nishida T, von Mehren M. Gastrointestinal stromal tumours. Nat Rev Dis Primers. 2021;7(1):22.
5. Sun Y, Yue L, Xu P, Hu W. An overview of agents and treatments for PDGFRA-mutated gastrointestinal stromal tumors. Front Oncol. 2022;12:927587.
6. Wong N, Garcia-Petit C, Dangoor A, Andrew N. A literature review and database of how the primary KIT/PDGFRA variant of a gastrointestinal stromal tumour predicts for sensitivity to imatinib. Cancer Genet. 2022;268-269:46-54.
7. Joensuu H, Rutkowski P, Nishida T, Steigen SE, Brabec P, Plank L, et al. KIT and PDGFRA mutations and the risk of GI stromal tumor recurrence. J Clin Oncol. 2015;33(6):634-42.
8. Joensuu H, Wardelmann E, Sihto H, Eriksson M, Sundby Hall K, Reichardt A, et al. Effect of KIT and PDGFRA Mutations on Survival in Patients with Gastrointestinal Stromal Tumors Treated with Adjuvant Imatinib: An Exploratory Analysis of a Randomized Clinical Trial. JAMA Oncol. 2017;3(5):602-9.
9. Jones RL, Serrano C, von Mehren M, George S, Heinrich MC, Kang YK, et al. Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumours: Long-term efficacy and safety data from the NAVIGATOR phase I trial. Eur J Cancer. 2021;145:132-42.
10. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003;21(23):4342-9.
11. Grellety T, Kind M, Coindre JM, Italiano A. Clinical activity of regorafenib in PDGFRA-mutated gastrointestinal stromal tumor. Future Sci OA. 2015;1(4):FSO33.
12. Farag S, Somaiah N, Choi H, Heeres B, Wang WL, van Boven H, et al. Clinical characteristics and treatment outcome in a large multicentre observational cohort of PDGFRA exon 18 mutated gastrointestinal stromal tumour patients. Eur J Cancer. 2017;76:76-83.
13. Tornillo L. Gastrointestinal stromal tumor - an evolving concept. Front Med (Lausanne). 2014;1:43.
14. Tatsuo Kanda TI, Takahiro Taguc. Gastrointestinal stromal tumor with a platelet-derived growth factor receptor-alpha mutation. Gastrointest Stromal Tumor. 2019; (2):2.
15. Li Y, Teng Y, Wei X, Tian Z, Cao Y, Liu X, et al. A rare simultaneous coexistence of epithelioid gastrointestinal stromal tumors and schwannoma in the stomach: a case report. DiagnPathol. 2019;14(1):116.
16. Corless CL, Schroeder A, Griffith D, Town A, McGreevey L, Harrell P, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol. 2005;23(23):5357-64.
17. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, et al. Kinase Mutations and Imatinib Response in Patients with Metastatic Gastrointestinal Stromal Tumor. J Clin Oncol. 2023;41(31):4829-36.
18. Dileo P, Pricl S, Tamborini E, Negri T, Stacchiotti S, Gronchi A, et al. Imatinib response in two GIST patients carrying two hitherto functionally uncharacterized PDGFRA mutations: an imaging, biochemical and molecular modeling study. Int J Cancer. 2011;128(4):983-90.