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KRAS G12C mutation in NSCLC in a small genetic center: insights into sotorasib therapy response potential

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Lung cancer remains a significant health challenge, characterized by aberrant tissue growth within the pulmonary system. Early carcinogenic events often involve genomic instability and the emergence of a mutator phenotype. In this study, we aimed to explore the mutator phenotype in 89 patients diagnosed with non-small-cell lung cancer (NSCLC). RNA isolation from formalin-fixed paraffin-embedded (FFPE) tissue samples was performed using the Promega ReliaPrep RNA Miniprep System, facilitating gene amplification relevant to cancer through the Archer® FusionPlexComprehensiveThyroid and Lung (CTL) kit. Next-generation sequencing (NGS) on the Illumina NextSeq platform enabled comprehensive analysis of target areas. Utilizing Archer Analysis software, secondary analyses involving data cleansing, alignment, and variant/fusion identification were executed against the human reference genome hg19 (GRCh37). Expression patterns were visualized using HeatMap graphics. Our findings revealed a notable presence of KRAS gene mutations in approximately 20% of NSCLC patients. Among these mutations, the G12C variant was predominant at 50%, followed by G12V and G12D variants at 11.2% each. Notably, patients harboring the G12C variant responded favorably to sotorasib medication. These results underscore the importance of mutational profiling and targeted therapeutic approaches in managing NSCLC, particularly highlighting the promising efficacy of sotorasib in G12C-mutated cases.

Keywords KRAS G12C mutation, Non-small-cell lung cancer, Sotorasib

Non–small cell lung cancer (NSCLC) refers to a spectrum of diseases, with varying genetic landscapes influencing patient outcomes and therapeutic responses. A mutation in the Kirsten rat sarcoma proto-oncogene (KRAS) is the most prevalent of the several oncogenic drivers. They are the cause of around 3% of squamous cell carcinomas and up to 25% of adenocarcinomas[1,2]. Activation of certain pathways, including the RAF-MEK-ERK pathway, maintains aberrant cell survival and proliferation when KRAS is active. Discordant findings have been reported on the prognostic significance of KRAS mutations in NSCLC and how they affect treatment results. Some research suggests that people with KRAS mutations might not benefit as much from chemotherapy[3], but no concrete evidence has been found to link the two[4,5]. There are also disagreements over how co-mutations in KRAS affect immunotherapy efficacy. A retrospective study has revealed a noteworthy correlation between co-mutations in the STK11/LKB1 genes and reduced overall and progression-free survival in patients with KRAS-mutant NSCLC undergoing immunotherapy[6]. These contradictory findings emphasize the genetic and phenotypic variation among KRAS-mutant NSCLC[7–9] and result from the complex nature of KRAS mutations. The KRAS G12C mutation stands out among them because it causes a genetically unique subtype of NSCLC, accounting for around 14% of cases that progress. This subgroup continues to be infamously resistant to traditional medications despite advances in therapy, which presents a major therapeutic challenge[10]. This specific mutation continually triggers downstream signaling pathways, including the RAF-MEK-ERK cascade, which results in unchecked cell division and growth[10]. Those with KRAS mutations, namely G12C, are distinct from those with other oncogenic driver mutations in NSCLC, such as epidermal growth factor receptor (EGFR)

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and anaplastic lymphoma kinase (ALK)[10,11]. It's interesting to note that KRAS-mutated NSCLC has a favorable response to first-line immunotherapy, which is not typical of other targetable mutant subtypes[12,13].

Before sotorasib was discovered, NSCLC with KRAS G12C mutations could only be treated with authorized medications if the disease did not have any targetable mutations. Usually, the first conventional treatment used was immunotherapy, either by itself or in combination with platinum-based chemotherapy. This sometimes resulted in the cancer progressing even though it raised the median overall survival[14,15]. While second-line drugs, such as docetaxel by itself or in combination with ramucirumab, demonstrated some efficacy, they were unable to address the underlying KRAS mutation[16]. Treatment for advanced NSCLC with KRAS G12C mutations has advanced dramatically since sotorasib was approved by the FDA. Patients who have advanced after at least one cycle of therapy now have new hope thanks to this innovative technique, which completely rethinks the norm for how treatments are delivered. With the advent of direct KRAS inhibitors like sotorasib, it has become more crucial than ever to understand the genomic settings of KRAS mutations. Here we offer a thorough analysis of a small cohort of KRAS-mutant NSCLC patients, evaluating each mutation subtype. The aim of our study is to emphasize the importance of mutational profiling and targeted treatment approaches in NSCLC and to state that sotorasib may be a promising drug, especially in cases with G12C mutation.

Materials and methods

Study subjects and clinical samples

Tissue samples from paraffin blocks of patients who attended the Division of Medical Genetics at Umraniye Education and Research Hospital, University of Health Sciences, between 2020 and 2022 and were diagnosed with non-small cell lung cancer were used in the study. Genes covered by the panel included *AKT1*, *ALK*, *BRAF*, *CTNNB1*, *DDR2*, *EGFR*, *ERBB2*, *FGFR1*, *GNAS*, *HRAS*, *IDH1*, *IDH2*, *KRAS*, *MAP2K1*, *NRAS*, *PIK3CA*, *RET*, and *ROS1*. And looked at were the fusions of *ALK*, *AXL*, *BRAF*, *CCND1*, *EGFR*, *FGFR1*, *FGFR2*, *FGFR3*, *MET*, *NRG1*, *NTRK1*, *NTRK2*, *NTRK3*, *PPARG*, *RAF1*, *RET*, *ROS1*, *THADA*. Additionally, expressions of *ALK*, *AXL*, *BRAF*, *CALCA*, *CCND1*, *EGFR*, *FGFR1*, *FGFR2*, *FGFR3*, *KRT7*, *KRT20*, *MET*, *NTRK1*, *NTRK2*, *NTRK3*, *PTH*, *RET*, *ROS1*, *SLC5A5*, *THADA*, *TTF1* genes were investigated.

RNA isolation and next-generation sequencing

RNA isolation from the primary sample (FFPE) was performed with the Promega ReliaPrep RNA Miniprep System for amplification of disease-associated genes/gene regions/fusions. Samples with a concentration of at least 10 ng from the isolated RNA samples were included in the study. Then samples' RNA was converted to cDNA using reverse transcriptase enzyme, using First Strand cDNA Synthesis kit. 1 µl of cDNA sample was placed in real time (BIO RAD^{R}) PCR device. The samples with QC value of 22–28 were placed in IlluminaNextSeq next generation sequencing (NGS) device. Raw data transferred to Archer Analysis platform were first evaluated in terms of Data Quality (fusions Fusion QC value Thershold ≥ 10, variants variations QC value Thershold ≥ 10). The human reference genome hg19 (GRCh37) was used for alignment. The barcodes contained both the molecular barcode and the patient index. The "HeatMap" image is used to show expression levels. Before the raw data was submitted to the Archer Analysis platform, the quality of the data was evaluated. After these measures were looked at, the samples that were judged appropriate were introduced to the analytic flow and evaluated about the diagnosed sickness. The analytical flow was filtered to exclude changes in the tumor type found by considering the patient's clinical data. After the lists were filtered, changes were made and classified according to information from guidelines and databases, along with specifics regarding diagnosis, prognosis, and treatment. A categorization has been made, considering the AMP/ASCO/AMP criteria and the evidence supporting the adjustments[17]. All methods were performed in accordance with the relevant guidelines and regulations.

Statistical analysis

Non-parametric Student's t-tests were conducted to evaluate the difference between G12C (Sotorasib response) group and Non-G12C (Sotorasib non-response) group following the Shapiro-Wilk test to verify normal distribution. Chi-square and/or Fisher's exact tests were used to evaluate sex differences between G12C variants and non-G12C variants. Instead of multiple chi-square tests, single-sample chi-square tests were performed individually. Fisher's exact test was applied to the cases where over 20% of the expected values were below 5. An adjusted P value of less than 0.05 was considered a significant difference. All statistical analyses were performed using GraphPad Prism 8.3.1 software (GraphPad Software, La Jolla California USA).

Results

The study included 89 subjects with a mean age of 60.08 ± 10.79 years. Among the NSCLC samples analyzed, 20.2% (18 samples) exhibited a KRAS gene mutation. Gene mutation frequencies associated with NSCLC are shown in (Fig. 1). The recorded mutation rates for other genes were 6.74% for the EGFR gene (Fig. 2), 3.37% for the EML4-ALK gene (Fig. 3a), 2.25% for the EML-ALK fusion, 2.25% for the BRAF gene, 2.25% for the FGFR3-TACC3 fusion (Fig. 3b), 2.25% for the MAP2K1 gene, 2.25% for the IDH1 gene, 1.12% for the KRAS and NRAS genes, 1.12% for the KRAS and EGFR genes, 1.12% for the HRAS gene, 1.12% for the RET gene, and 1.12% for the PIK3CA gene. Additionally, 56% of patients had other unidentifiable alterations.

The most common KRAS mutation was G12C, observed in 50% of the cases (Fig. 4). Other notable KRAS mutations included G12D (11.2%) (Fig. 5) and G12V (11.2%) (Fig. 6). The medication Sotorasib showed a high degree of favorable response in patients with the KRAS G12C variant (Table 1).

There were no significant differences in the mean ages between patients with different KRAS mutation variants: G12C (Sotorasib response) group ($n = 9$) 64.67 ± 7.176 and Non-G12C (Sotorasib non-response)

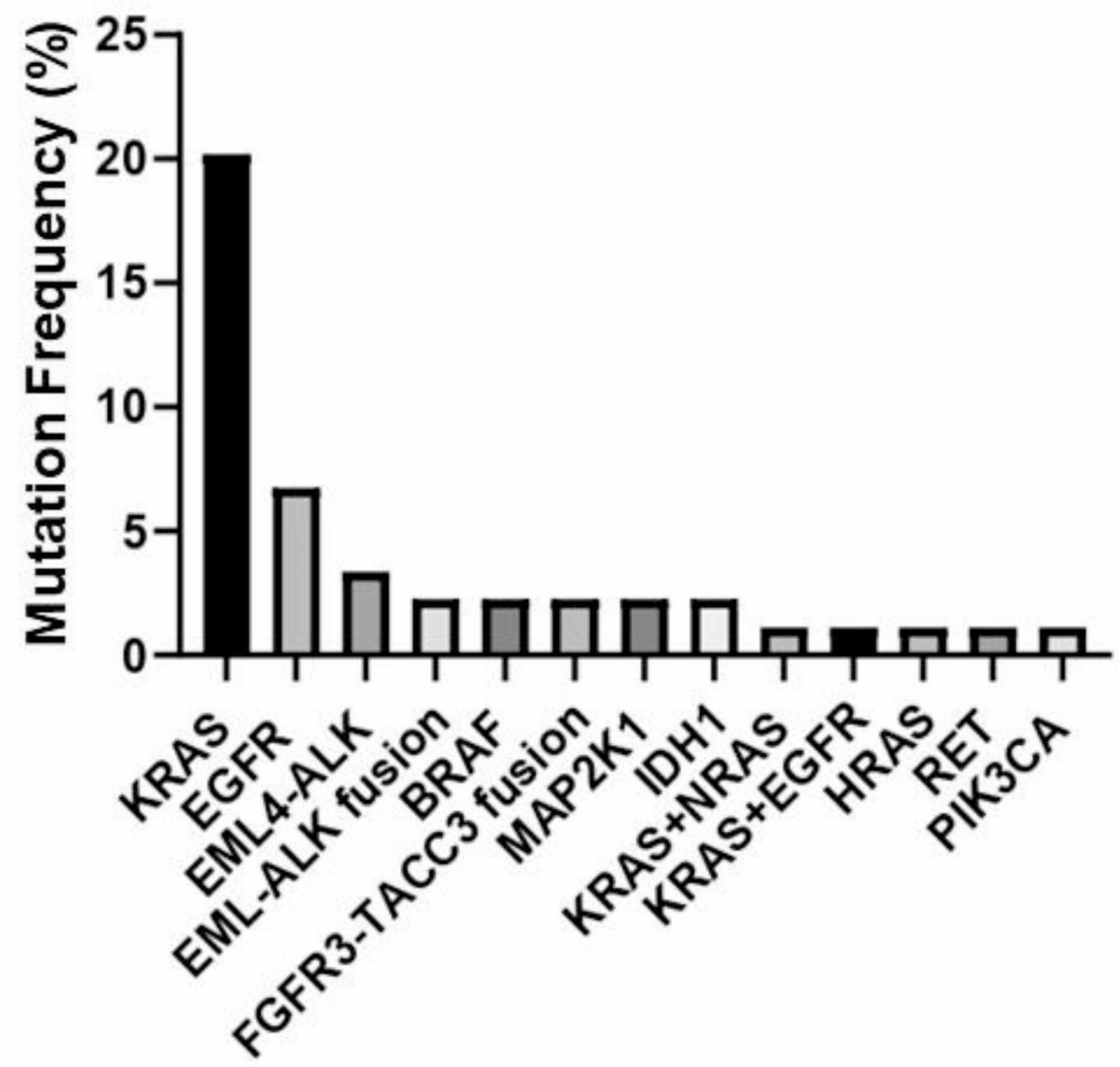


Fig. 1. Mutation rates of the genes associated with NSCLC.

group ($n=9$) 67.22 ± 6.852 ($P=0.8990$). Gender comparison between patients with KRAS G12C and non-G12C mutations also showed no significant differences: G12C M/F: 5/4 and Non-G12C M/F: 6/3 ($P=62.87$).

Discussion

Our study found that *KRAS* mutations were present in 20% of cases with NSCLC. It is nearly consistent with the recent report that adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are among the cancer types that have been reported to carry *KRAS* mutations in 25% of cases[18]. A *KRAS* mutation may also be associated with a worse prognosis in NSCLC, according to studies. *KRAS* mutation was a substantially bad predictive factor for lower overall and disease-free survival in a meta-analysis of patients with NSCLC[19]. Concurrent *KRAS* and *EGFR* mutations were the most prevalent combination of mutations[20]. *EGFR* mutations and *KRAS* mutations were commonly shown to be related[20]. *KRAS* mutation and *EGFR* mutation were mutually exclusive, with the majority of mutations occurring in adenocarcinomas[21]. A particular and shared molecular route in the formation of lung adenocarcinomas may be represented by the co-mutation of *KRAS*/*EGFR*. Clinical ramifications might be substantial from this, and this patient subgroup might benefit substantially from a combination of targeted treatment aimed at both routes[21].

The proportion of *EGFR* mutations in our research was 6.74%. The frequency of *EGFR* mutation was lower than the 44% *EGFR* mutation rate reported in a recent retrospective study of cytology samples in lung cancer[22]. Such different results may be related to differences in geographic location, *EGFR* variant, and method used.



Fig. 2. Mutations of *EGFR* from NSCLCs non-sensitive to *Sotorasib*.

EGFR gene mutations are now the most extensively researched issue in the field of developing medications for NSCLC. Many healthy and malignant cells have the EGFR protein on their surface. It binds to a material known as epidermal growth factor, which promotes cell division. Cancer cells may proliferate when the *EGFR* gene is altered, and a mutant version of the protein is produced. Additionally, it may increase the likelihood that these cancer cells may spread to different body regions[23]. In this study, the mutation frequency was observed as 5.62%, with co-mutation and fusion of *ALK* and *EML* (Echinoderm Microtubule-Associated Protein-Like) being the third most common next to *EGFR*. The fusion of the genes *ALK* and *EML* is another gene rearrangement that is considered an oncogenic driver[24]. The N-terminal half of EML4 fuses with the intracellular kinase domain of ALK when a minor inversion occurs inside the short arm of chromosome 2, inv (2) (p21p23)[24]. Other driver mutations essentially prevent *EML-ALK* fusion[25]. Studies showed that a distinctive pattern of gene expression and the activation of certain signaling pathways were linked to *EML-ALK* fusion. This may result in a decrease in apoptosis and differentiation, an increase in cellular invasion, migration, and proliferation, and the promotion of certain lung cancer morphologic traits[26]. Additionally, there was a substantial correlation found between the *BRAF* gene mutation and the advanced stage in a recent study[27]. Overall, *BRAF*-mutated patients were less



Fig. 3. (a) Co-mutation of EML4-ALK from NSCLCs non-sensitive to *sotorasib*. (b) Co-mutation of FGFR3-TACC3 from NSCLCs non-sensitive to *Sotorasib.*



Fig. 4. Mutations of *KRAS G12C variant* from NSCLCs sensitive to *Sotorasib*.

likely to undergo chemotherapy than wild-type patients, and there was a significant correlation with the type of treatment they got[28]. Instead of being a target for a particular treatment, *BRAF* mutations may be a negative predictive factor for chemotherapy. However, a few percent of patients with BRAF mutations were observed in the current study.

In the present study, in a few percent of cases of NSCLC, there was a mutation in the *MAP2K1* gene as well. According to a recent study, *MAP2K1* is an important B7 family member-related gene in NSCLC. MAP2K1 is found to be an important differential protein in NSCLC and a critical component of the ErbB/MAPK signaling pathway[29]. The current investigation also revealed a few percent of mutations in the isocitrate dehydrogenase (*IDH*) genes[30], and co-mutation between the NRAS and KRAS genes. Previous research has reported that *IDH1* mutation in lung adenocarcinoma is associated with an extensive smoking history, older age, and metastasis[30]. However, patients with NSCLC who have cancers that are *NRAS/KRAS* mutant may have a very low prognosis[31]. Moreover, a few percent of the Harvery-Ras (*HRAS*) gene mutations, the Rearranged During Transfection gene (*RET*) gene mutations, and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene mutations were detected in our study as well. It has been demonstrated that *KRAS* and *HRAS* mutations are mutually exclusive in different tumor types[32]. The phosphatidylinositol 3-kinase (PI3K)/AKT route and the mitogen-activated protein kinase (MAPK) pathways are in charge of cell division, growth, and survival under typical circumstances. A *RET* mutation indicates an increase in function[33]. *PIK3CA* mutant NSCLC may constitute a unique clinical entity, despite the lack of data indicating an increase in survival in patients with the mutations and the features of the patients who have them[34].

Even though *KRAS* mutations have long been known to play a part in the development of cancer, no potent anti-cancer therapies that specifically target *KRAS* mutations have been developed until recently[35]. Only little effectiveness was indicated by the 11% and 12% response rates that MEK inhibition elicited, which were notably erratic[36,37]. Recently, sotorasib, a tiny medication that permanently inhibits the KRAS G12C-mutant protein, has demonstrated encouraging phase I results in patients with *KRAS* G12C-mutated NSCLC: 88.1% disease control and a 32.2% response rate[38,39]. While there are a lot of variances in response duration, resistance mechanisms, and outcomes for individuals with *KRAS*-mutated NSCLC, the findings are generally very positive. These

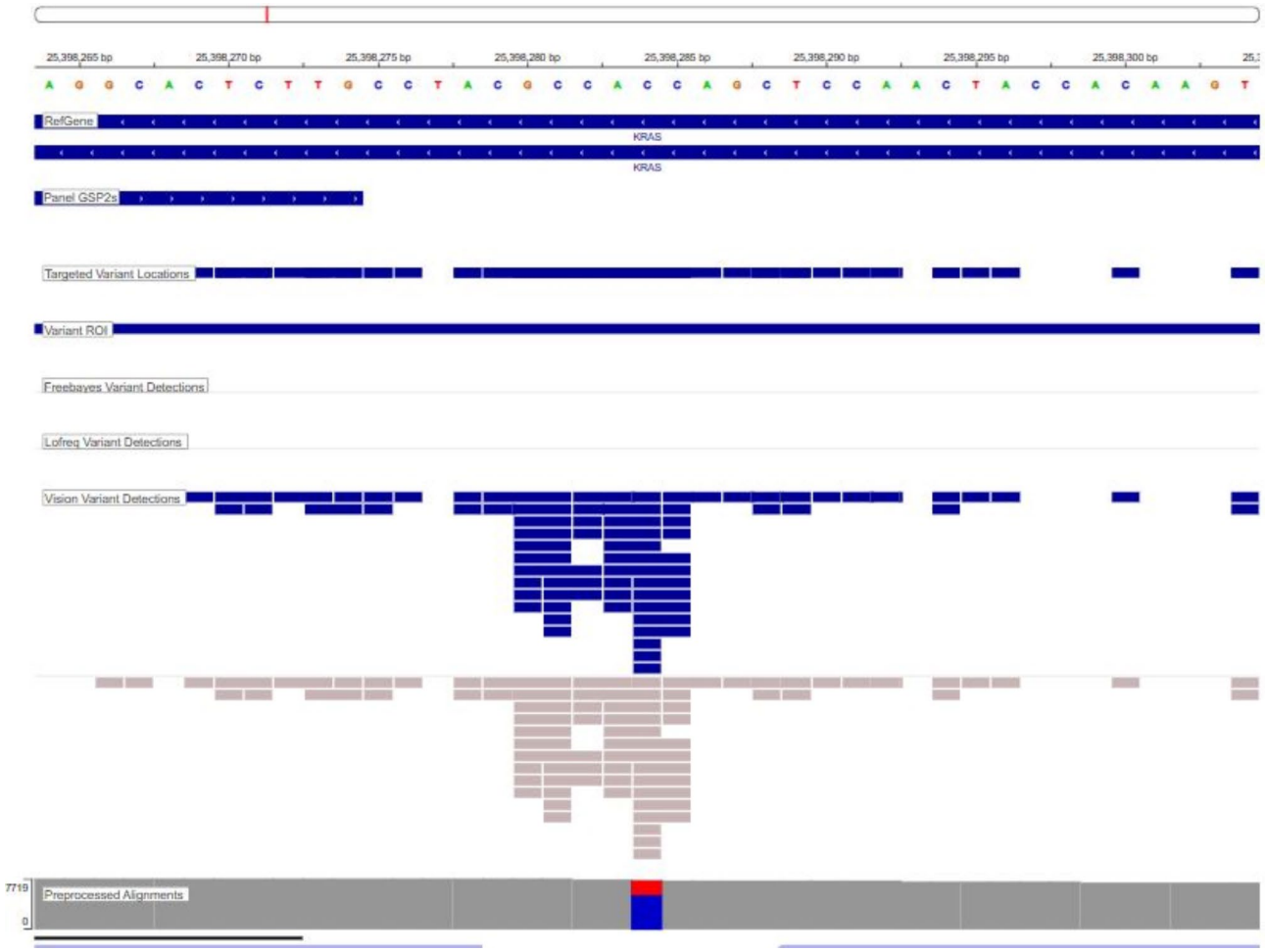


Fig. 5. Mutations of *KRAS G12D variant* from NSCLCs non-sensitive to *Sotorasib*.

parameters may all be influenced by specific co-mutations that were present at the time of diagnosis. Our study clarifies mutational heterogeneity that may contribute to the results of previous KRAS-targeted studies and may impact the future efficacy of KRAS inhibitors tailored to specific subtypes.

There are several limitations to the study. First, a very limited sample size of 89 individuals with NSCLC was used in the investigation. The results may not be as applicable to a larger group of NSCLC patients due to this small sample size. Second, the accuracy of gene expression and mutation analysis may be impacted by the introduction of biases associated with RNA quality and integrity that may arise from the use of FFPE tissue samples. Furthermore, the use of Archer Analysis and Illumina NextSeq software may induce platform-specific biases that affect how the sequencing data is interpreted. Finally, the favorable response to sotorasib observed in G12C-mutated cases should be further validated in larger, more diverse cohorts to confirm its efficacy and rule out any selection bias.

Conclusions

Our study sheds light on the significance of mutational profiling in addressing the complexities of NSCLC. Through comprehensive genomic analysis, we identified a substantial prevalence of *KRAS* gene mutations, with the G12C variant being predominant. Importantly, our findings highlight the therapeutic potential of sotorasib, particularly in patients harboring the G12C mutation, with an impressive response rate observed. These results underscore the importance of personalized medicine approaches tailored to individual mutational profiles in NSCLC management. In the future, continued research in this area promises to improve treatment strategies and outcomes for patients with this challenging disease.

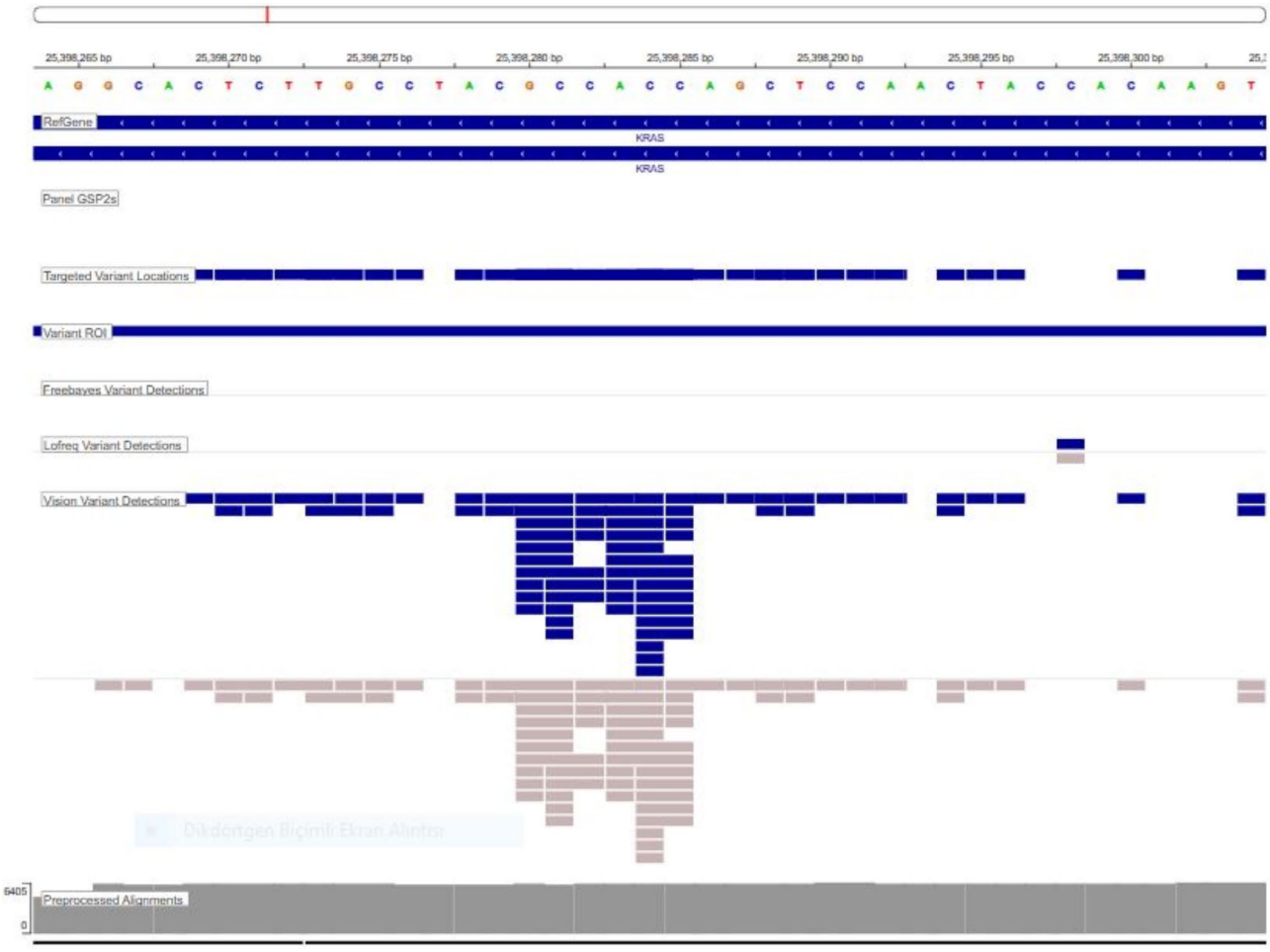


Fig. 6. Mutations of *KRAS G12V variant* from NSCLCs non-sensitive to *Sotorasib*.

Ratio (%)	Gene	Transcript	Variant	Protein	COSMIC	ASCO / AMP	Sotorasib Response
10.1	KRAS	NM_004985.4	34G > T	Gly12Cys	COSM516	TierIA	(+)
10.1	KRAS	NM_004985.4 NM_004985. NM_004985.4 NM_004985.4 NM_004985.3	34_35delinsTT 175G > A 35G > A 35G > T 35G > C	Gly12Phe Ala59Thr Gly12Asp Gly12Val Gly12Ala	COSM512 COSM1562187 COSM521 COSM520 COSM522	TierIIC TierIIC TierIIC TierIIC TierIIC	(-)
1.12	KRAS NRAS	NM_004985.4 NM_002524.4	436G > A 38G > A	Ala146Thr Gly13Asp	COSM19404 COSM573	TierIIC TierIIC	(-)
1.12	KRAS EGFR	NM_004985.4 NM_005228.4	35G > T 2386G > A	Gly12Va Gly796Ser	COSM520 COSM20891	TierIIC TierIID	(-)
6.74	EGFR	NM_005228.4	2709_2710inv	Val904Ile	-	TierIII	(-)
2.25	BRAF	NM_004333.4	1799T > A	Val600Glu	COSM476	TierIA	(-)
1.12	HRAS	NM_005343.3	38G > T	Gly13Val	COSM489	TierIII	(-)
1.12	RET	NM_020630.4	2694_2705del	Asp898_Glu901del	COSM962	TierIIC	(-)
2.25	IDH1	NM_005896.3	532G > A	Val178Ile	COSM97131	TierIV	(-)
2.25	MAP2K1	NM_002755.3	171G > T	Lys57Asn	COSM1235478	TierIII	(-)
1.12	PIK3CA	NM_006218.4	1571G > A	Arg524Lys	-	TierIII	(-)
3.37	EML4::ALK	NM_019063.5 NM_004304.5	chr2:42491871,chr2:29448431	-	COSF1296	TierIA	(-)
2.25	EML::ALK	NM_019063.5 NM_004304.5	chr2:42552694,chr2:29446394	-	COSF409	TierIA	(-)
2.25	FGFR3::TACC3	NM_000142.4 NM_006342.2	chr4:1808661, chr4:1741429	-	-	TierIB	(-)
50. 6	Other						

Table 1. Patients' genetics and response information to the Sotorasib medication.

Data availability

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

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Author contributions

Author Contributions GH contributed to the concept of the study, acquired, analyzed, and interpreted the data, and took the lead in writing the manuscript. ME, MHY, SC, and MO contributed to the concept of the study, collection of the data, and interpretation of the results. All authors provide this consent.

Declarations

Competing interests

The authors declare no competing interests.

Consent to participate

The participants have already given informed consent.

Ethics approval

This study was approved by the Ethical Committee of Umraniye Training and Research Hospital (Ethics No: B.10.1.TKH.4.34.H.GP.0.01/271, 10/08/2023), School of Medicine, University of Health Sciences, Istanbul, Türkiye.

Additional information

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