Original Research

**p.G12C KRAS** mutation prevalence in non-small cell lung cancer: Contribution from interregional variability and population substructures among Hispanics

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**ABSTRACT**

**Background:** The KRAS exon 2 p. G12C mutation in patients with lung adenocarcinoma has been increasing in relevance due to the development and effectiveness of new treatment medications. Studies around different populations indicate that regional variability between ethnic groups and ancestries could play an essential role in developing this molecular alteration within lung cancer.

**Methods:** In a prospective and retrospective cohort study on samples from lung adenocarcinoma from 1000 patients from different administrative regions in Colombia were tested for the KRAS p.G12C mutation. An analysis of STR populations markers was conducted to identify substructure contributions to mutation prevalence.

**Results:** Included were 979 patients with a national mean frequency for the KRAS exon 2 p.G12C mutation of 7.97% (95%CI 7.27-8.67%). Variation between regions was also identified with Antioquia reaching a positivity value of 12.7% (95%CI 9.1-16.3%) in contrast to other regions such as Bogota DC (Capital region) with 5.4% (95%CI 4.0-7.2%) (p-value = 0.00262). Furthermore, Short tandem repeat

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**Keywords:** Non small cell lung cancer Molecular epidemiology KRAS Population markers

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population substructures were found for eight markers that strongly yielded association with KRAS exon 2 p.G12C frequency reaching an adjusted R2 of 0.945 and a p-value of < 0.0001.

**Conclusions:** Widespread identification of KRAS exon 2 p.G12C mutations, especially in cases where NGS is not easily achieved is feasible at a population based level that can characterize regional and national patterns of mutation status. Furthermore, this type of mutation prevalence follows a population substructure pattern that can be easily determined by population and ancestral markers such as STR.

**Introduction**

Non-small-cell lung cancer (NSCLC) accounts for ~85% of primary lung cancers, the most common subtypes being adenocarcinoma (ADC) and squamous cell carcinoma (SCC) [1]. Recently, genetic profiling has identified driver mutations, believed to contribute to early carcinogenesis, in over 80% of ADC cases and ~47% of SCC cases. In the last two decades, understanding driver mutations have evolved, from reports of KRAS mutations in ADC in 1987 [2], to reports of fusions between KIF3B and RET in 2012 [3]. Therapies targeting driver mutations have provided promising promise in relevant populations, including those with mutations in EGFR, BRAF, Her2, and MET, as well as fusion genes involving ALK, ROS1, and RET, among others [4]. It is also important to consider mutations in tumor suppressor genes (TSGs) associated with NSCLC, including TP53, STK11, and PTEN, since they frequently coincide with other oncogenic mutations, affect prognosis, and potentially impact the response to immunotherapy [5].

KRAS is one of the most frequently mutated genes in NSCLC. KRAS mutations are associated with smokers and with a more aggressive phenotype [6–10], and the frequency varies among distinct populations, accounting for approximately 25% in Whites and <10% in East Asians [6]. Recently, Liu et al. characterized 17,113 NSCLC specimens using next-generation sequencing (NGS) and classified them based on presence and types of KRAS; across the entire cohort, 27% of samples harbored a KRAS mutation, being the most frequent variants the exon 2 p.G12C (40%), followed by exon 2 p.G12V (19%) and exon 2 p.G12D (15%) [7]. The prevalence of KRAS mutations was 37.2% among adenocarcinoma and only 4.4% in squamous cell carcinomas [11]. In addition, most ADCs carrying KRAS mutations present a High Tumor Mutation Burden (TMB, defined by> 10 mts/Mb), which varies across the different KRAS variants, being most common in exon 2 p.G13X (68.3%) and least common in exon 2 p.G12D (43.2%) [7]. In the same dimension, PD-L1 expression also varied among KRAS NSCLC, finding that the exon 2 p.G12C alteration was the most likely to be PD-L1 positive, with 65.5% TPS >1%, and the most likely to be PD-L1 high, with 41.3% TPS >50%. KRAS is associated with various commutations; STK11 is especially relevant, which is altered in 36% of cases (more in the exon 2 p.G13X variant 36.2% and less in the exon 2 p.G12D 14.2%) [7,11]. In contrast, TP53 mutations were more frequent in KRAS wild-type NSCLC (73.6%) [7].

In less than five years, the availability of novel therapies has transformed the landscape of KRAS mutant NSCLC, and a target that was once considered “undruggable” now has several possibilities tested in clinical trials and many others in progress. There are essentially four novel approaches to target KRAS that can be divided into targeted therapies and immunotherapy, potentially combined [12–14]. A novel class of KRAS inhibitors that specifically block the exon 2 p.G12C mutation through direct interaction with cysteine residue and a somewhat broader approach using a pan-KRAS inhibitor that two do not attempt to inhibit specific mutations. The compounds AMG-510 (Sotorasib, Amgen, Thousand Oaks, CA) and MRTX849 (Adagrasib, Mirati Therapeutics, San Diego, CA) was developed to target the KRAS exon 2 p.G12C mutation [14,15]. These specific inhibitors locked exon 2 p.G12C mutation in an inactive state, hampering the oncogenic signals and allowed the normal function of remained wild-type KRAS [12,15,16]. In a phase I study, 32.2% (19 out of 59) of sotorasib-treated patients presented objective response, and 88.1% (52 out of 59) presented disease control [12]. In phase I and II study, 94% (17 out of 18) of adagrasib-treated NSCLC patients presented with disease control, and the objective response was not yet available (KRYSAL-1 study; ClinicalTrials.gov identifier: NCT03785249) [14].

Although the differences in somatic mutation patterns between ADCs from patients of different ethnicities, the landscape of ancestry effects on the lung cancer genomes for the Latin American populations has not been comprehensively described, recently, Carrot-Zhang et al. performed an extensive ancestry analysis from tumor samples in an admixed population of NSCLC patients from México and Colombia [16], finding that native ancestry was positively correlated with mutations EGFR, and anti-correlated with mutations in KRAS and STK11. Furthermore, the ancestry effect on KRAS mutation was independent of smoking, and the frequency of mutations in this gene was only 12%. In contrast, Cavagna et al. recently reported a prevalence of KRAS mutations of 25.3% from the analysis of 844 Brazilian patients with NSCLC [17].

To establish the population differences among Hispanics, we present the analysis of KRAS mutations among 979 Colombian NSCLC patients from 19 regions of the country, which allowed us to assess the contribution from interregional variability and population substructures.

**Material and methods**

**Study design and patients**

The methods of the study were performed in two stages. In the first one, the conditions of the method for detecting the exon 2 p.G12C mutation of the KRAS gene by Digital PCR (dPCR) were standardized. Likewise, Next Generation Sequencing (NGS) methods were also standardized for the detection of the exon 2 p.G12C mutation in the KRAS gene using DNA samples extracted from paraffin-embedded tissue (FFPE) and cfDNA extracted from plasma (Supplementary Fig. 1). On the other hand, in the second stage, the KRAS exon 2 p.G12C mutation was detected in DNA samples extracted from paraffin-embedded tissue (FFPE) in 979 duplicate samples from patients with NSCLC selected from the biobank of the Foundation for Clinical and Applied Cancer Research (FICMAC, Bogotá, Colombia) (Supplementary Fig. 2). Tumor DNA from tumor FFPE and cfDNA samples from 61 patients with NSCLC cancer were retrospectively and prospectively collected; each case required a paired sample from tumor and plasma. Samples from patients were considered negative for EGFR, ALK, and ROS1, have enough tumor tissue for analysis, and availability of the liquid sample. Once the samples were collected, the standardization of the method for detecting the exon 2 p.G12C mutation of the KRAS gene by ddPCR and NGS techniques was carried out following the methods described below.

**Sample preparation**

In FFPE samples, a minimum of 2 sections of 4–6 μm with a minimum of 20% tumor representation was taken for DNA isolation with the ReliaPrep™ FFPE gDNA Miniprep System - Promega kit, and the manufacturer’s recommendations were followed. In plasma samples, 2 ml
were taken for cfDNA isolation with the MagMAX™ Total Nucleic Acid Isolation kit -Invitrogen- and the manufacturer’s recommendations were followed. Tumor DNA and cfDNA samples are already isolated or isolated de novo. All samples were quantified by spectrophotometric methods with the NanoDrop 2000 / 2000c and Qubit® 3.0 Fluorometer Catalog Number Q33216 kits; by the same token, the manufacturer’s recommendations were followed.

Detection of KRAS exon 2 p.G12C mutation

The digital droplet PCR (ddPCR) technique was performed with the PrimePCR™ ddPCR™ Mutation Detection Assay Kit: KRAS G12C - BioRad in the QX200 Droplet Digital PCR System, then the data were analyzed with the QuantaSoft™ Software. Subsequently, the DNA samples that had the exon 2 p.G12C mutation detected by the digital PCR technique also were determined by NGS technique with the preparation of the library with Oncomine™ Focus Assay - Thermo Fisher Scientific, following the manufacturer’s recommendations. The data obtained by this technique were analyzed by Oncomine™ Reporter software and an in-house bioinformatics pipeline. Comparisons between ddPCR and NGS were conducted on 60 samples.

Furthermore, and in order to determine nation prevalence and variation, we retrospectively analyzed 1000 tumor DNA samples obtained from FFPE of patients with NSCLC archived in the Foundation for Clinical and Applied Cancer Research (Bogotá, Colombia). In addition, all cases should be negative for EGFR and ALK and had a known status for PD-L1 expression.

Detection of KRAS exon 2 p.G12C mutation in tumor DNA samples

The tumor DNA was quantified, the digital PCR technique was performed with the PrimePCR™ ddPCR™ Mutation Detection Assay Kit: KRAS G12C - BioRad in the QX200 Droplet Digital PCR System, then the data were analyzed with the QuantaSoft™ Software, and the manufacturer’s recommendations were followed.

Statistical analysis

For statistical analysis, the percentage was used to describe categorical variables, and medians were used to describe continuous variables. Fisher’s exact test and χ² test were used for the association between KRAS mutations and the clinicopathologic data. A stepwise multiple linear regression was conducted. KRAS exon 2 p.G12C regional prevalence were the dependent variable and, as the independent variable, the allelic frequencies of regionally reported CODIS short tandem repeats (STR), including all 23 markers and their alleles. These markers correspond to 23 STR that are located across the human genome, are not related to the KRAS gene, and have been amply used in the forensic sciences for individual identification and population characterization. They are amplified by PCR and identified by capillary electrophoresis. The largest known study to characterize these markers among different regions in Colombia, included over 11.000 samples and was the data source for the model [18]. Collinearities were manually excluded from the model. All analyses were performed with R (version 4.0.2, The R Foundation).

Results

Validation of mutation detection methods

Next-generation sequencing was performed paired with ddPCR in 60 tissue samples for the validation of the ddPCR diagnostic test. In the NGS group, a total of 8 samples revealed a KRAS exon 2 p.G12C mutation compared to 10 in the ddPCR samples. Discordant samples were subjected to Sanger sequencing to evaluate possible false negatives. Considering NGS and Sanger sequencing and a mutation prevalence of 13.3%, ddPCR in tissue samples revealed a sensitivity of 100% (95%CI 63 - 100%) and a specificity of 96.2% (95%CI 88.6 - 99.5%). A positive predictive value of 80% (95%CI 44 - 97%) and a negative predictive value of 100% (95%CI 93 – 100%) were also estimated.

Detection in patient samples

A total of 979 samples among 19 regions were included in the analysis. Regions and samples were excluded from the initially screened 1000 samples if the region of collection lacked enough samples to be representative or the region did not contribute to any number of samples. Eight samples were considered the threshold value, considering that one sample was expected to be detected among those 8 considering an estimated prevalence of 12.5%. Sample and region inclusions and exclusions are presented in Fig. 1. 78 occurrences of a KRAS exon 2 p.G12C mutation were detected among sampled NSCLC patients, yielding a national prevalence of 7.97% (95%CI 6.27–9.66%). Differences in several regions were also observed. Antioquia, revealed a mutational prevalence of 12.7% (95%CI 9.1–16.3%) in contrast to other regions such as Bogota DC (Capital region) with 5.4% (2.7–8.2%) and Bolivar with 2.4% (95%CI 0.7–2.7%) (p value = 0.00262 for Bolivar and Bogota compared to Antioquia). Fig. 2 depicts regional prevalence and geographic distribution of regional positivity and national average. These results indicate a variety of mutation prevalence among regions and highlight a possible population substructure that presents with enriched or depleted KRAS exon 2 p.G12C mutational prevalence.

Population markers and KRAS exon 2 p.G12C mutations

Multiple linear regression identified a series of markers that yielded a relevant R2 value and p-value. The regional allelic frequencies of D13S317 12, D19S433 13.2, D15S1656 11, D15S1656 16, D22S1045 15, D22S1045 17, D2S1338 21, D2S441 12, D2S441 12.2, D7S820 11, D13S317 12, D19S433 13.2, D1S1656 11, D1S1656 16, D22S1045 15, D22S1045 17, D2S1338 21, D2S441 12, D2S441 12.2, D7S820 11, D8S1179 13, FGA 19, TH01 6, TPOX × 9, Via 20. A trade-off between these two parameters was taken to construct a model with relatively few predictors and good predictive performance. Fig. 3 represents a relationship between the number of predictors and adjusted R2 and their combined association and the same metric, with an adjusted R2 of 0.945 and a p-value of <0.0001, a model of 8 predictors was chosen. Table 1 depicts chosen markers and their corresponding coefficients in the constructed model.

Since the representation of all regions could not be achieved, KRAS exon 2 p.G12C mutation prevalence in non-represented regions could not be obtained; allelic frequencies for chosen STR were imputed in the model to obtain these values. Fig. 4 presents measured frequencies and estimated ones across all the national territories. This model indicates a high intranational and interregional variation with an estimated
Fig. 1. CONSORT Diagram of analyzed samples and regions.

Fig. 2. Regression Model selection based on adjusted R2 in relationship to number and combinatory of predictors. The left panel depicts adjusted R2 in relationship with number of markers. The right panel identifies as a black square including several combinations of markers and their impact on adjusted R2, represented in the Y axis.
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prevalence reaching up to 20.04% in La Guajira. Other regions behaved around the median value, others tending to be low, behaving similarly as seen in the measured regions.

Discussion

The genomic landscape of LUADs is strikingly varied in Latin American patients with mixed ancestries. Previous studies demonstrated that native ancestry was correlated with somatic driver alterations, including \textit{EGFR} and \textit{KRAS} mutations that small molecule inhibitors can effectively target to prolong survival [19, 20], and TMB and \textit{STK11} are potential prognostic biomarkers in lung cancer patients [21, 22]. Cava-gna et al. recently reported a frequency of \textit{KRAS} mutations in an open population of patients with NSCLC from Brazil, with the exon 2 p.G12C variant being 9% of the cases. They also found that \textit{KRAS} mutations were associated with smoking status (current or quitter) and worse overall survival [17]. Our study demonstrated a national prevalence of 7.97% of \textit{KRAS} exon 2 p.G12C mutations, like that previously reported in Brazil. We also identified that certain regions presented with lower [2.4% (95% CI 0–7.2%); 5.4% (95% CI 2.7 – 8.2%)] and higher frequencies [12.7% (95% CI 9.1 – 16.3%)] than the national average. In addition, evaluating the association of these prevalence and population markers based on short tandem repeats (CODIS STR), we also identified that eight markers and their allelic frequencies were highly associated with regional positivity.

A recent review reported that \textit{KRAS} mutations are present in 18%–32% of lung adenocarcinoma, 12.8% of large cell carcinoma, 10% of adenosquamous carcinomas, and 1.6%–7.1% of squamous-cell carcinomas in White patients [23]. Moreover, African-American patients with NSCLC are more frequently identified with \textit{KRAS} mutations than White patients. The frequency of \textit{KRAS} mutations in Western populations with lung adenocarcinoma is about 26% and about 6% in the squamous-cell carcinoma population. In Asian patients, the frequency of \textit{KRAS} mutations is 11.2% of patients with NSCLC [24]. According to The Cancer Genome Atlas, \textit{KRAS} mutations are found in 33% of lung adenocarcinoma [4]. Our previous study involving 5738 NSCLC cases reported 14% of \textit{KRAS}-mutated cases in Latin American except for Brazil (Argentina, Mexico, Colombia, Peru, Costa Rica, and Panama) [19]. The detection of the \textit{KRAS} exon 2 p.G12C mutation is not homogeneous for all diagnostic tests. Our results highlight that different performances can be obtained from different methodologies. PCR is a cost-saving alternative that can be implemented in low to middle-income countries where the costs of conducting NGS on all newly diagnosed patients remain prohibitive. If required, confirmatory sequence analysis is left for a minority of patients, optimizing resources while identifying candidates for newly available medications [12, 14].

This study also indicates that the prevalence of \textit{KRAS} exon 2 p.G12C prevalence follows a pattern that relies on population composition and explains to some degree, the variation in different regions around Latin America and the world. It was also conducted on a nation with high ancestral population diversity, leading to different population substructures within the same geographical regions. In addition, administrative regions tend to follow a pattern of ancestral migration and ethnic composition that serve as the perfect comparative scenario, thus serving

| Table 1
| Multiple regression model and performance. |
|---|---|---|---|
| Residuals | Min | 1q | Median | 3q | Max |
| Coefficients | Intercept | 7.971 | 10.48 | 0.761 | 0.4687 |
| | D22S1045_15 | –26.755 | 13.11 | –2.04 | 0.0756 |
| | D22S1045_17 | 172.169 | 16.27 | 10.581 | < 0.0001 |
| | D2S441_12 | 95.645 | 19.65 | 4.867 | 0.001 |
| | D2S441_12.3 | –324.392 | 52.49 | –6.180 | < 0.0001 |
| | D7S820_11 | –111.804 | 15.20 | –7.352 | < 0.0001 |
| | D8S1179_13 | –26.201 | 12.53 | –2.091 | 0.069 |
| | TH01_6 | 127.062 | 18.21 | 6.975 | < 0.0001 |
| | Vwa_20 | 540.786 | 139.33 | 3.882 | 0.004 |
| Residual standard error | 1.21 in 8 degrees of freedom |
| Multiple R2 | 0.973 |
| Adjusted R2 | 0.946 |
| F statistic | 36.26 in 8 degrees of freedom |
| p-value | < 0.0001 |

Fig. 3. Geographic distribution and regional mutation prevalence.
as comparative micro ethnic scenarios [25]. Since phenotypes for mixed individuals fall outside the traditional Asian, Black, White, or Hispanic characterizations, molecular ancestral and population markers offer a higher degree of substructure identification. Four contributors for ancestral populations for Colombia have been identified. These are Native America, European, Mediterranean and African. Among these four, each has varying degree of contribution to certain regions. In addition, there are also representation from different subpopulations among these large contributors. In the case of native American, in whom Asian ancestry has been identified, Andes Piedmont contributions, that originated from Ecuador and northern Peru have been identified in the southern and central regions of Colombia. The northern regions tend to represent Chibcha and Paez ancestries that are indigenous to the region. Considering European ancestries, Central and southern Spain markers have been identified across all sampled regions. Minor contributions from Portuguese and Western Spain were found in the northern and western region of the country. Moreover, Eastern Mediterranean identifiers are present in the central region, whereas Sephardic in the eastern and northern region, coinciding with Antioquia, the region with one of the highest number of positive p.G12C mutants. Finally, African contribution comprised in the vast majority of West African descent. Interestingly, African markers are vastly represented in the coastal regions and are rather scarce in the center of the nation. These findings indicate that a clear population substructure from different ancestries exists in Colombia [25].

These substructures are important in determining the impact on molecular phenotypes in lung cancer. Regional variation of KRAS exon 2 p.G12C and STR was identified within regions confirming the hypotheses that population substructures that better characterize average prevalence exist. Population factors such as tobacco consumption has been associated with KRAS positivity [2]. Interestingly this variable was not taken into consideration since tobacco consumption rates are relatively stable among included administrative regions in Colombia [26], suggesting a higher contribution of genetic aspects.

Since the prevalence of KRAS exon 2 p.G12C mutations and their variation within other nations has not widely been determined, the estimation of the individual population using STR allelic frequencies becomes useful. These frequencies have been widely studied since they are used in individual identification and paternity testing [27–29]. This approach of identifying associations with surrogate markers that are more available than KRAS exon 2 p.G12C mutations for specific populations allows for health care systems around the world to estimate their regional positivity rate with the aims of resource allocation.

Since representative samples of certain regions could not be obtained in this study, estimation of KRAS exon 2 p.G12C mutations yielded an exciting picture of mutation distributions in these regions. Sucre, located in the northern and costal region, yielded a similar prevalence as Antioquia, closing on 14%. Since regional closeness could potentially correspond to migratory patterns, it would be expected that the prevalence would fall nearby. La Guajira follows a similar pattern reaching close to 20% with a much wider confidence interval that encompasses Sucre and Antioquia, indicating that similar prevalence would be expected.

This study is not free of limitations. Since the characterization of KRAS exon 2 p.G12C mutations was conducted with ddPCR, a possibility for error in diagnosis, with an increased overestimation, is worth mentioning. Furthermore, model selection could have followed fewer STRs, warranting less overfitting by sacrificing performance. This, in turn, warrants that these results should be validated in other populations in which a similar analysis is conducted. Finally, the decision to
determine regional variability based on administrative regions could have potentially decreased population precision by including more individuals, but due to data availability, especially STR frequencies, this compromise had to be made.

Conclusion

In conclusion, implementing a screening program of KRAS exon 2 p. G12C mutation in LUAD patients with ddPCR could be considered based on good diagnostic performance metrics compared to NGS. In addition, this type of mutation follows a population substructure distribution pattern that determines their prevalence. Furthermore, by denoting these substructures with population markers such as STRs’, the prevalence of KRAS exon 2 p. G12C mutations can be inferred.

CRediT authorship contribution statement

Alejandro Ruiz-Patiño: Conceptualization, Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. July Rodríguez: Data curation, Methodology, Writing – review & editing. Andrés F. Cardona: Conceptualization, Formal analysis, Supervision, Validation, Writing – original draft. Jenny Ávila: Data curation, Methodology, Writing – review & editing. Pilar Archila: Data curation, Methodology, Writing – review & editing. Hernán Carranza: Data curation, Methodology, Writing – review & editing. Carlos Vargas: Data curation, Methodology, Writing – review & editing. Jorge Otero: Data curation, Methodology, Writing – review & editing. Oscar Arrieta: Supervision, Project administration, Writing – original draft. Carolina Zatarain-Barrón: Supervision, Project administration, Writing – original draft. Carolina Sotelo: Supervision, Project administration, Writing – review & editing. Camila Ordonez: Supervision, Project administration, Writing – original draft. Juan Esteban García-Robledo: Supervision, Project administration, Writing – review & editing. Leonardo Rojas: Data curation, Writing – review & editing. Maritza Bermúdez: Methodology, Writing – review & editing. Tatiana Gámez: Methodology, Writing – review & editing. Diana Mayorga: Methodology, Writing – review & editing. Luis Corrales: Validation, Writing – review & editing. Claudio Martín: Validation, Writing – review & editing. Gonzalo Recondo: Validation, Writing – review & editing. Luis Mas: Validation, Writing – review & editing. Suraj Samtani: Validation, Writing – review & editing. Alessandro Russo: Validation, Writing – review & editing. Feliciano Barrón: Validation, Writing – review & editing. Christian Rolfo: Conceptualization, Project administration, Writing – original draft. Rafael Rosell: Conceptualization, Project administration, Writing – original draft.

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Declaration of Competing Interest

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Supplementary materials

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