South Russian Journal of Cancer. 2025. Vol. 6, No. 4. P. 36-45
https://doi.org/10.37748/2686-9039-2025-6-4-4
https://elibrary.ru/FVFBDU
Oncology, radiotherapy
EXPERIENCE EXCHANGE

CHEK2 p.Ile157Thr (c.470T>C) mutation in non-small cell lung cancer: regional experience

A. M. Sigal[1,2]✉, M. G. Gordiev[3], B. F. Mostyukov[4], N. Z. Sattarova[1], S. V. Zinchenko[1]

[1] Kazan Federal University, Kazan, Russian Federation
[2] The Republican Clinical Oncological Dispensary named after Prof. M.Z. Sigal, Kazan, Russian Federation
[3] Moscow Research and Practical Center for Laboratory Diagnostics, Moscow, Russian Federation
[4] Kazan State Medical Academy – Branch Campus of the Russian Medical Academy of Continuous Professional Education, Kazan, Russian Federation
✉ Sigal2@mail.ru

ABSTRACT

Purpose of the study. To determine the frequency and co-occurrence with major somatic drivers of the germline CHEK2 p.Ile157Thr mutation in patients with non-small cell lung cancer (NSCLC) in the Republic of Tatarstan.

Patients and methods. Targeted next-generation sequencing (NGS) of key oncogenes was performed on tumor tissue from 151 patients. A bibliographic search was carried out manually in Google Scholar and PubMed using the terms "CHEK2 I157T," "p.Ile157Thr," "c.470T>C," "NSCLC," "germline," "NGS," among others; search formulations were refined with the aid of artificial intelligence, followed by mandatory manual verification. Statistical analysis was performed in SPSS v18.0. Proportions were compared using Fisher's exact test with a significance threshold of $p < 0.05$.

Results. The p.Ile157Thr variant was identified in 12 patients (7.9 %); all cases (100 %) were histologically confirmed adenocarcinomas. A positive family history of malignant tumors was recorded in 2 patients (16.7 %), and multiple primary malignancies in 2 patients (16.7 %). Concomitant driver mutations were detected in 8 patients (66.7 %): EGFR in 5 (62.5 %), while 3 patients (37.5 %) harbored mutations in KRAS (12.5 %), NRAS, and BRAF, respectively. In 4 patients (33.3 %), p.Ile157Thr was the sole molecular event. In a comparison of carriers versus non-carriers of CHEK2 p.Ile157Thr, no statistically significant differences were observed in stage distribution or in the frequency of co-occurring driver alterations (Fisher's exact test, $p > 0.05$).

Conclusion. The germline CHEK2 p.Ile157Thr (c.470T>C) variant was identified in a subset of patients with lung adenocarcinoma and in several cases was accompanied by somatic driver mutations. The obtained data refine the frequency of this variant in the studied population and describe the molecular characteristics of tumors in carriers, providing a basis for further evaluation of the potential clinical relevance of CHEK2 in NSCLC.

Keywords: CHEK2, p.Ile157Thr, c.470T>C, I157T, lung cancer, non-small cell lung cancer, NGS, next-generation sequencing, germline mutations, hereditary mutations

For citation: Sigal A. M., Gordiev M. G., Mostyukov B. F., Sattarova N. Z., Zinchenko S. V. CHEK2 p.Ile157Thr (c.470T>C) mutation in non-small cell lung cancer: regional experience. South Russian Journal of Cancer. 2025; 6(4): 36-45. https://doi.org/10.37748/2686-9039-2025-6-4-4 EDN: FVFBDU

For correspondence: Albert M. Sigal – Cand. Sci. (Medicine), Associate Professor of the Department of Surgery, Kazan Federal University, Kazan, Russian Federation; thoracic surgeon, oncologist of the Oncology Department No. 1, The Republican Clinical Oncological Dispensary named after Prof. M.Z. Sigal, Kazan, Russian Federation
Address: 29 Sibirskiy trakt, Kazan, 420029, Russian Federation
E-mail: Sigal2@mail.ru
ORCID: https://orcid.org/0000-0002-5918-4225, eLibrary SPIN: 6457-2742, AuthorID: 909681

Compliance with ethical standards: the study followed the ethical principles set forth by the World Medical Association Declaration of Helsinki, 1964, ed. 2013. The study protocol was reviewed and approved by the Ethics Committee of Kazan Federal University, Kazan, Russian Federation (protocol extract No. 52, August 28, 2025). Written informed consent was obtained from all participants prior to their inclusion in the study.

Funding: this work was not funded.

Conflict of interest: the authors declare that there are no obvious and potential conflicts of interest associated with the publication of this article.

The article was submitted 22.07.2025; approved after reviewing 10.11.2025; accepted for publication 28.11.2025.

Южно-Российский онкологический журнал. 2025. Т. 6, № 4. С. 36-45
https://doi.org/10.37748/2686-9039-2025-6-4-4
https://elibrary.ru/FVFBDU
3.1.6. Онкология, лучевая терапия
ОБМЕН ОПЫТОМ

Мутация CHEK2 p.Ile157Thr (c.470T>C) при немелкоклеточном раке легкого: региональный опыт

А. М. Сигал[1,2]✉, М. Г. Гордиев[3], Б. Ф. Мостюков[4], Н. З. Саттарова[1], С. В. Зинченко[1]

[1] Казанский (Приволжский) федеральный университет, г. Казань, Российская Федерация
[2] Республиканский клинический онкологический диспансер Министерства здравоохранения Республики Татарстан им. проф. М.З. Сигала, г. Казань, Российская Федерация
[3] Московский научно-практический центр лабораторных исследований Департамента здравоохранения, г. Москва, Российская Федерация
[4] Казанская государственная медицинская академия – филиал ФГБОУ ДПО «Российская медицинская академия непрерывного профессионального образования» Министерства здравоохранения Российской Федерации, г. Казань, Российская Федерация

✉ Sigal2@mail.ru

РЕЗЮМЕ

Цель исследования. Определить частоту и сочетание с основными соматическими драйверами герминальной мутации CHEK2 p.Ile157Thr у пациентов с немелкоклеточным раком легкого (НМРЛ) в Республике Татарстан.

Пациенты и методы. Панельное NGS-секвенирование ключевых онкогенов выполнено в опухолевом материале 151 пациента. Библиографический поиск проводился вручную в Google Scholar, PubMed по сочетаниям «CHEK2 I157T», «p.Ile157Thr», «c.470T>C», «NSCLC», «germline», «NGS» и др.; формулировки уточнялись с помощью искусственного интеллекта при обязательной ручной верификации. Статистическую обработку выполняли в SPSS v18.0; для сравнения долей применяли точный критерий Фишера, уровень значимости $p < 0,05$.

Результаты. Вариант p.Ile157Thr выявлен у 12 (7,9 %) пациентов: у 100 % подтверждена гистологически аденокарцинома. Семейный анамнез злокачественных опухолей зафиксирован у 2 (16,7 %) пациентов, множественные первичные новообразования – у 2 (16,7 %). Сопутствующие драйверные мутации обнаружены у 8 (66,7 %): EGFR – у 5 (62,5 %), у 3 (37,5 %) была обнаружена одна из мутаций KRAS (12,5 %), NRAS и BRAF соответственно. У 4 (33,3 %) p.Ile157Thr было единственным молекулярным событием. При сравнении носителей и неносителей CHEK2 p.Ile157Thr по стадиям заболевания и частоте сопутствующих драйверов статистически значимых различий не выявлено (точный критерий Фишера, $p > 0,05$).

Заключение. Герминальный вариант CHEK2 p.Ile157Thr (c.470T>C) выявлен у части пациентов с аденокарциномой легкого и в ряде случаев сочетался с соматическими драйверными мутациями. Полученные данные уточняют его частоту в исследуемой популяции и описывают молекулярные особенности опухолей у носителей, что может быть использовано в дальнейших исследованиях клинического значения CHEK2 при НМРЛ.

Ключевые слова: CHEK2, p.Ile157Thr, c.470T>C, I157T, рак легкого, немелкоклеточный рак легкого, NGS, секвенирование нового поколения, герминальные мутации, наследственные мутации

Для цитирования: Сигал А. М., Гордиев М. Г., Мостюков Б. Ф., Саттарова Н. З., Зинченко С. В. Мутация CHEK2 p.Ile157Thr (c.470T>C) при немелкоклеточном раке легкого: региональный опыт. Южно-Российский онкологический журнал. 2025; 6(4): 36-45. https://doi.org/10.37748/2686-9039-2025-6-4-4 EDN: FVFBDU

Для корреспонденции: Сигал Альберт Мойшевич – к.м.н., доцент кафедры хирургии ФГАОУ ВО «Казанский (Приволжский) федеральный университет», г. Казань, Российская Федерация; торакальный хирург, врач-онколог онкологического отделения №1 ГАУЗ «Республиканский клинический онкологический диспансер МЗ Республики Татарстан им. проф. М.З. Сигала», г. Казань, Российская Федерация
Адрес: 420029, Российская Федерация, г. Казань, Сибирский тракт, д. 29
E-mail: Sigal2@mail.ru
ORCID: https://orcid.org/0000-0002-5918-4225, eLibrary SPIN: 6457-2742, AuthorID: 909681

Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по этике при ФГАОУ ВО «Казанский (Приволжский) федеральный университет», г. Казань, Российская Федерация (выписка из протокола заседания № 52 от 28.08.2025). Информированное согласие получено от всех участников исследования.

Финансирование: финансирование данной работы не проводилось.

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Статья поступила в редакцию 22.07.2025; одобрена после рецензирования 10.11.2025; принята к публикации 28.11.2025.

BACKGROUND

Lung cancer is one of the most aggressive malignant neoplasms and remains among the leading causes of cancer morbidity (2nd place – 2.1 million new cases) and mortality (1st place – 1.8 million deaths annually) worldwide [1]. The etiology of the disease represents a complex interplay between exogenous factors and genetic alterations, including both hereditary predisposition and sporadic somatic mutations [2]. Smoking is considered the predominant exogenous driver, accounting for 80–90 % of cases among men and 60–70 % among women [3].

Despite advances in diagnostic and therapeutic strategies, the prognosis of lung cancer remains poor, underscoring the need for novel treatment approaches based on a deeper understanding of the molecular mechanisms of carcinogenesis. In this context, precision medicine, grounded in the identification of tumor-specific genetic characteristics, has emerged as a pivotal direction in modern oncology, transforming therapeutic paradigms and improving the likelihood of long-term remission.

A major breakthrough in the molecular characterization of non-small cell lung cancer (NSCLC) was the discovery of the role of EGFR (epidermal growth factor receptor) mutations in the early 2000s, which not only revealed the pathogenetic heterogeneity of the disease but also laid the foundation for the development of targeted therapies [4]. The introduction of high-throughput next-generation sequencing (NGS) technologies into clinical practice enabled the detection of rare and previously unrecognized genetic variants associated with oncogenesis. This led to the identification of a wide spectrum of driver mutations, including alterations in ALK, ROS1, KRAS, BRAF, MET, RET, and other genes, each defining a unique biological tumor subtype requiring an individualized therapeutic approach [5].

Although most molecular alterations in NSCLC are somatic and associated with exposure to exogenous carcinogens, recent evidence highlights the contribution of hereditary mutations. In a large cohort study by Sorscher S. et al., including 7,788 unrelated patients with lung cancer who underwent uniform NGS testing (panel of up to 159 genes, mean sequencing depth ≈ ×350), pathogenic or likely pathogenic variants were identified in 14.9 % of patients (1,161/7,788). The most frequent mutations included BRCA2 (2.8 %), CHEK2 (2.1 %), ATM (1.9 %), TP53 (1.3 %), BRCA1 (1.2 %), EGFR (1.0 %), APC (0.9 %), and PALB2 (0.5 %). Notably, 61.3 % of all detected variants were found in genes involved in DNA damage repair, and 95 % were classified as clinically significant [6]. In the present review, we focus on germline variants in the CHEK2 (Checkpoint Kinase 2) gene, which plays a key role in maintaining genomic stability and regulating the cell cycle, with specific emphasis on the CHEK2 p.Ile157Thr (c.470T>C) missense variant.

The involvement of CHEK2, a gene encoding the serine/threonine kinase CHK2, a central component of the DNA double-strand break response pathway, was first demonstrated by Bell D. W. et al. in 1999. In their study, a germline 1100delC mutation was identified in a family with Li–Fraumeni syndrome. Loss of CHK2 kinase activity was shown to impair phosphorylation of key proteins (p53, BRCA1, CDC25C), compromising checkpoint activation and DNA repair, and thereby predisposing to early-onset and multiple malignancies. These findings established CHEK2 as a tumor suppressor gene [7].

In 2002, two independent studies extended this concept to a broader population context. Meijers-Heijboer H. et al. demonstrated that 1100delC confers an approximately twofold increased risk of breast cancer in women and nearly a tenfold increase in men in non-BRCA families [8]. Vahteristo P. et al. reported that the same allele accounts for a considerable proportion of familial clusters of breast cancer and is associated with loss of CHK2 expression in tumor tissue [9].

In 2004, both the allelic and nosological spectra were expanded: Kilpivaara O. et al. were the first to associate the missense variant I157T, which retains partial kinase activity, with a moderate increase in breast cancer risk, demonstrating that not only truncating mutations but also functionally defective amino acid substitutions are involved in tumorigenesis [10].

Cybulski C. et al. simultaneously investigated three Polish founder alleles of CHEK2 – the truncating 1100delC and IVS2+1G>A variants, as well as

the missense p.Ile157Thr – and showed that their carriage increases the risk not only of breast cancer but also of malignancies of the colon, prostate, thyroid, and kidney, thereby firmly establishing the gene as a multi-organ, moderate-penetrance cancer susceptibility factor [11].

The best-studied CHEK2 mutations remain p.Ile157Thr and 1100delC, both associated with an increased risk of several malignancies, including breast cancer [12], colorectal cancer [13], and prostate cancer [11]. However, the limited evidence on the role of CHEK2 in lung cancer pathogenesis leaves a substantial gap in understanding the molecular basis of the disease and restricts the potential for applying personalized therapeutic approaches in affected carriers of this genetic alteration.

CHEK2 exhibits pronounced geographic heterogeneity. In Northern Europe, the truncating founder mutation c.1100delCpredominates, with population carrier frequencies approaching approximately 1 % in the United Kingdom and the Netherlands, gradually decreasing toward Southern Europe, where it is detected only sporadically. In Eastern (and partly Central) Europe, the distribution shifts toward the missense variant p.I157T (c.470T>C), with heterozygous carriers comprising around 5 % of the general population in Poland, Latvia, Hungary, and Russia, and 2–3 % in the Czech Republic, Slovakia, and Germany, making it the most common regional CHEK2 variant. In Asian populations, European founder mutations are virtually absent: in a cohort of 8,085 Chinese women, the total frequency of pathogenic CHEK2variants did not exceed 0.3 %, with half represented by a novel nonsense allele p.Y139X. Independent datasets demonstrated an association between the recurrent missense variant p.H371Y and breast cancer susceptibility [14]. Taking into account this regional distribution, the present study focused on the p.Ile157Thr (c.470T>C) variant as the most prevalent and clinically relevant CHEK2 alteration in Eastern Europe.

A neighboring region ethnographically related to the Republic of Tatarstan – the Republic of Bashkortostan – demonstrates a similar Eastern European pattern: in a cohort of 977 breast cancer patients and 1,069 controls, the p.Ile157Thr (c.470T>C) missense variant was the most frequent (~5 % in both cohorts), whereas c.1100delC and the splice mutation c.444+1G>A were detected in only 0.4 % of cases, and a large deletion del5395 occurred in 1.23 % of patients and only 0.09 % of healthy controls [15].

Thus, the rationale for selecting CHEK2 for investigation is determined by its pivotal role in the DNA damage response system and the high prevalence of the p.Ile157Thr variant in the Eastern European population.

Purpose of the study: to determine the frequency and co-occurrence with major somatic drivers of the germline CHEK2 p.Ile157Thr mutation in patients with NSCLC in the Republic of Tatarstan.

PATIENTS AND METHODS

The present study included patients with NSCLC treated at the Republican Clinical Oncology Dispensary of the Ministry of Health of the Republic of Tatarstan named after Prof. M. Z. Sigal. In total, tumor tissue samples from 151 patients were analyzed. The median age was 67 years, and the mean age was 64 years. There were 70 men (46.3 %) and 81 women (53.7 %). The ethnic composition of the cohort was homogeneous (Russians and Tatars), reflecting the demographic structure of the region. The smoking history of the patients demonstrated a typical distribution for an NSCLC cohort and included both current/former smokers and never-smokers.

Tumor samples were analyzed using next-generation sequencing (NGS) on the NextSeq 2000 platform (Illumina) with the KAPA HyperPETE LC Fusion Panel and KAPA HyperChoice panels (Roche Diagnostics).

The genomic analysis included:

A DNA panel comprising 43 genes associated with DNA repair, cell cycle regulation, and oncogenesis:

- *ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CDK12, CHEK1, CHEK2, EPCAM, FANCL, MLH1, MSH2, NBN, NF1, PALB2, PMS2, RAD51B, RAD51C, RAD51D, RAD54, STK11, TP53, KRAS, NRAS, BRAF, EGFR, ERBB2, PIK3CA, MET (ex14), KIT, POLE, KEAP1, PDGFRA, ESR1, EPCAM, IDH1/2*.

- An RNA panel aimed at detecting transcriptional alterations and fusion transcripts in 17 key oncogenes: *ALK, AXL, BRAF, EGFR, FGFR1–3, MET, NRG1, NTRK1–3, PDGFRA, PDGFRB, PPARG, RET, ROS1*.

Annotation and interpretation of identified variants were performed using the *ClinVar*, *gnomAD*, and *dbSNP* databases, which allowed differentiation between somatic and germline alterations. The *CHEK2 p.Ile157Thr (c.470T>C, rs17879961)* variant was identified as a known germline variant registered in these databases and classified as pathogenic according to ACMG (2015) criteria. Detection of this variant in tumor tissue reflects the presence of an inherited mutation rather than a purely somatic event, which is supported by its annotation in population and clinical variant databases.

The literature search was performed manually in Google Scholar and PubMed using combinations of the following keywords: "CHEK2", "p.Ile157Thr", "c.470T>C", "NSCLC", "germline", "NGS", etc. At the stage of content analysis, interpretation of the articles, and stylistic optimization of the wording, the artificial intelligence system ChatGPT o3 was used, with mandatory manual verification and editing of each fragment.

Statistical analysis

Statistical processing was carried out using SPSS software (version 18.0). Fisher's exact test was applied for comparison of categorical variables. Differences were considered statistically significant at $p < 0.05$. Statistical analysis was limited to internal comparison of clinical and molecular characteristics between carriers and non-carriers of the CHEK2 p.Ile157Thr (c.470T>C) variant.

STUDY RESULTS

A germline CHEK2 mutation was identified in 12 patients (prevalence 7.95 %), and in all cases, the detected variant was c.470T>C (p.Ile157Thr, I157T). Histologically, all patients had lung adenocarcinoma of varying degrees of differentiation. The sex distribution was equal (6 men and 6 women), and the mean age was 65 years. Five individuals (41.7 %) were active or former smokers, whereas 7 patients (58.3 %) reported no history of smoking.

One female patient had been diagnosed in 2006 with right breast cancer (stage III, T3N1M1), for which she underwent radical mastectomy, chemotherapy, and external-beam radiation therapy. In 2024, a second primary tumor was identified a right upper lobe lung adenocarcinoma localized in a region of prior radiation changes. Tumor profiling revealed EGFR exon 19 deletion, a BRCA1 mutation, and the germline CHEK2 p.Ile157Thr (c.470T>C) variant.

Another female patient had been diagnosed in 2009 with papillary thyroid carcinoma (stage II, pT2N0M0) and underwent a thyroidectomy followed by radiation therapy. In 2016, she was diagnosed with left upper lobe lung adenocarcinoma (stage IIA, pT1N1M0), treated with extended lobectomy. In 2024, disease progression was documented, with metastases to the contralateral lung and submandibular salivary gland, along with the diagnosis of a third primary tumor – renal cancer. Molecular analysis of the lung tumor identified an EGFR exon 19 deletion and the germline CHEK2 p.Ile157Thr (c.470T>C) variant.

These two clinical observations demonstrate a phenotypic association between CHEK2 p.Ile157Thr carrier status and the development of multiple primary tumors of distinct localization, including malignancies of the thoracic and genitourinary systems, consistent with previously reported associations in CHEK2-positive individuals.

Analysis of disease stages revealed a distribution typical for NSCLC: early (stage I) and metastatic disease (stage IV) predominated, while intermediate stages (II–III) were less common (Fig. 1). The clinical course corresponded to patterns widely observed in NSCLC cohorts, with most patients presenting with localized or locally advanced disease, and the remainder with metastatic spread.

Additional somatic driver mutations were detected in 8 patients (66.7 %) (Fig. 2). The most frequent alterations involved EGFR, followed by less common changes in KRAS, NRAS, and BRAF. In two patients, EGFR-positive tumors co-occurred with TP53 or BRCA1 variants; a potential germline origin of the latter cannot be excluded because only tumor tissue was sequenced. In four patients (33.3 %), the CHEK2 p.Ile157Thr variant was detected in isolation, without accompanying somatic driver mutations.

The immunohistochemical profile of tumors was

consistent with lung adenocarcinoma: TTF-1 and CK7 positive, p40 negative, with Ki-67 ranging from 15 % to 60 %.

Comparison of disease stage distribution and frequency of somatic driver mutations between carriers and non-carriers of the CHEK2 p.Ile157Thr (c.470T>C) variant revealed no statistically significant differences (Fisher's exact test, $p > 0.05$).

DISCUSSION

The present study is one of the first in the Republic of Tatarstan aimed at identifying the germline CHEK2 p.Ile157Thr (c.470T>C) mutation and its co-occurrence with somatic driver alterations in patients with NSCLC. The analysis was performed using next-generation sequencing (NGS).

In the study by Kazakov A. M. et al., which included 90 patients with stage I–IIIA NSCLC, the authors conducted targeted sequencing of tumor tissue with parallel analysis of paired "normal" lung material, enabling a systematic description of the somatic mutational landscape of two histological subtypes (63 adenocarcinomas and 27 squamous cell carcinomas). The 78-gene panel encompassed both point mutations (e. g., *EGFR*, *KRAS*, *BRAF*) and gene rearrangements (e. g., *ALK*, *ROS1*, *RET*). Adenocarcinomas were dominated by TP53, KRAS, and EGFR alterations, with a range of rare but clinically meaningful events (including BRAF) that were consistent with global estimates. For CHEK2, rare somatic variants were reported predominantly in adenocarcinomas (mainly in exon 2), while germline status was not assessed and the p.Ile157Thr (I157T) allele was not detected. Thus, although the study provides relevant context for the somatic landscape of localized NSCLC and supports the value of expanded panels, our work fundamentally differs by focusing on the germline CHEK2 p.Ile157Thr variant and its prevalence and molecular associations in an Eastern European clinical cohort [16].

Research addressing the CHEK2 p.Ile157Thr (c.470T>C) variant as a hereditary risk factor for lung cancer is represented in the works of Brennan P. et al. [17], Cybulski C. et al. [18], and Wang Y. et al. [19], which demonstrated that I157T is associated with a reduced risk of squamous cell carcinoma of the lung, while no significant protective effect has been confirmed for adenocarcinoma. All three studies were conducted in European populations, where the I157T allele shows a minor allele frequency of approximately 4–5 %. The reported CHEK2 I157T carrier rate among lung cancer patients ranged from 1 % to 3 %, and approximately 5 % in the general population.

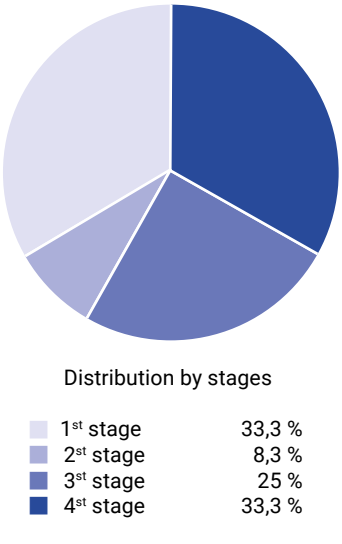

Fig. 1. Percentage distribution of patients with the CHEK2 p.Ile157Thr mutation by stage of lung cancer

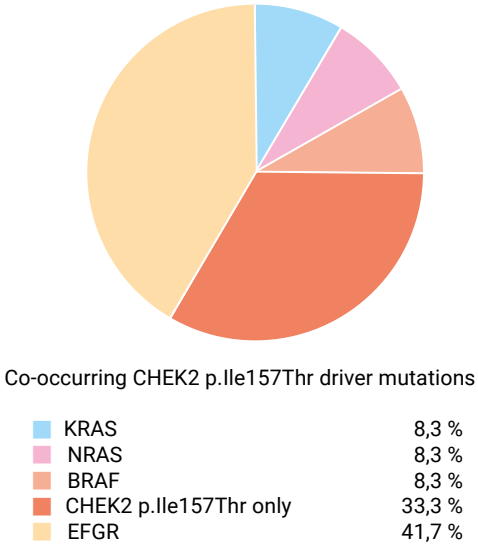

Fig. 2. Percentage distribution of patients with the CHEK2 p.Ile157Thr mutation according to the coexistence of lung cancer with driver mutations.

In our study, the p.Ile157Thr (c.470T>C) mutation was detected in 12 out of 151 patients, corresponding to a carrier frequency of 7.9 % (95 % CI: 4.6–13.4 %). All carriers were heterozygous, with an allele frequency of 3.98 % (95 % CI: 2.3–6.8 %).

All 12 carriers of the CHEK2 p.Ile157Thr (c.470T>C) variant were diagnosed with lung adenocarcinoma; squamous cell carcinoma and small cell carcinoma were not observed in the carrier subset. Historically, CHEK2 p.Ile157Thr has been associated with a protective effect primarily for squamous cell lung cancer, without a significant influence on adenocarcinoma risk. The higher proportion of carriers in the present study may reflect population-specific and histological characteristics, as well as the limited sample size.

Current evidence on the role of CHEK2 p.Ile157Thr (c.470T>C) in lung cancer remains based on a small number of studies, predominantly from 2007–2014. Large European NGS investigations focusing specifically on this variant and its somatic co-alterations have not yet been conducted.

In our cohort, 66.7 % of CHEK2 p.Ile157Thr carriers exhibited additional oncogenic events, most commonly EGFR alterations, and less frequently KRAS, BRAF, and NRAS mutations. This pattern reflects the expected mutation profile of lung adenocarcinoma, summarized in the review by Kharagezov D. A. et al., which discusses common point mutations (EGFR, KRAS) and rare but clinically relevant events (BRAF), whereas germline CHEK2 variants were not considered [20]. The observed co-occurrence of germline CHEK2 with common and rare drivers should be interpreted as hypothesis-generating. Validation requires larger multicenter cohorts, paired tumor–normal testing, and functional assays.

NGS remains essential for identifying such complex interactions. Accumulating data on the relationships between germline predisposition variants and somatic tumor profiles may help refine the biological role of CHEK2 and potentially support its incorporation as a prognostic or stratification marker in NSCLC precision oncology.

To date, only a limited number of large NGS datasets include both germline variants and somatic profiles in NSCLC with reported CHEK2 alterations. In a study by Zhang S. S. et al., 70 patients (1.15 %) carried pathogenic germline CHEK2 variants, and among them, 33 % (*n* = 23) were p.Ile157Thr carriers. Co-occurring somatic drivers included KRAS G12C/G12D (~40 %), EGFR ex19del/L858R (~25 %), and isolated cases of ALK, ROS1, RET, MET exon 14 skipping, and BRAF V600E [21]. However, the somatic spectrum was not stratified by specific CHEK2 alleles, including p.Ile157Thr (c.470T>C), limiting conclusions.

Mezquita L. et al. identified 547 patients (0.62 %) with any pathogenic CHEK2 variant, with somatic driver frequencies of EGFR 34 %, KRAS 21 %, and *ALK/ROS1/MET/BRAF* ~15 % combined; however, specific CHEK2 alleles were not detailed [22].

In a Chinese study by Zhou N. et al., germline CHEK2 mutations were identified in 89 individuals (1.8 %), but p.Ile157Thr (c.470T>C) was not observed, consistent with its low prevalence in Asian populations. Nonsense and truncating alleles (p.Y139*, K373fs) predominated. Among somatic drivers, EGFR alterations dominated (~55 %), KRAS occurred in <10 %, and ALK/ROS1/MET exon 14 events were rare [23].

Thus, CHEK2 I157T is rare in Asian cohorts and more frequent in North American datasets, although the multiethnic composition of these cohorts complicates population-specific interpretation. Without robust ancestry stratification, precise prevalence estimates for Eastern Europe remain uncertain. Importantly, no large NGS study has yet systematically examined the association between germline CHEK2 variants and somatic NSCLC drivers in Europe, particularly with focused attention on p.Ile157Thr (c.470T>C).

Therefore, the present regional NGS-based investigation from an Eastern European population provides the first data generated using contemporary molecular diagnostics on the prevalence of CHEK2 p.Ile157Thr (c.470T>C) and its co-mutation patterns in NSCLC.

At present, germline CHEK2 mutations are known to increase the risk of breast, colorectal, and prostate cancer, which is reflected in NCCN[1] guidelines [24, 25]. Enhanced surveillance protocols are

[1] National Comprehensive Cancer Network (NCCN) [Internet]. Available at: https://www.nccn.org – *Editorial note.*

recommended for carriers. However, in NSCLC, the role of CHEK2 remains poorly defined. CHEK2 is not included among hereditary risk genes in the NCCN NSCLC guidelines or in the low-dose CT lung cancer screening guideline [26, 27]. Only two germline contexts are clearly addressed: exclusion of germline EGFR p.T790M when detected in tumor tissue, and Li–Fraumeni syndrome (germline TP53), discussed in specific recommendations. Other driver loci (ALK, ROS1, MET, BRCA2, RB1, etc.) are considered exclusively therapeutic somatic targets, without guidance for family screening [27].

This creates a dual gap: carriers of CHEK2 variants do not receive lung cancer screening recommendations even in the presence of family history, while families with hereditary NSCLC patterns do not routinely undergo CHEK2 testing despite its relevance in other cancers. This imbalance underscores the need for further research into the contribution of CHEK2 – particularly p.Ile157Thr (c.470T>C) – to NSCLC carcinogenesis.

CONCLUSION

Analysis of this regional cohort of patients with non-small cell lung cancer demonstrates that the germline CHEK2 p.Ile157Thr (c.470T>C) variant occurs more frequently than suggested by international datasets and forms a distinct molecular context within these tumors. All identified carriers had lung adenocarcinoma, and most exhibited co-occurrence of the germline variant with somatic driver alterations typical for this subtype – predominantly EGFR mutations, and less frequently KRAS, BRAF, and NRAS. This indicates that, even in the presence of well-established “classical” somatic patterns, the disease profile may be influenced by the underlying hereditary background. The findings obtained using modern NGS approaches represent the first systematic data on the frequency and molecular environment of p.Ile157Thr in Eastern Europe and highlight an evident gap in the literature.

Comparative analysis of the clinical and molecular features of carriers and non-carriers of CHEK2 p.Ile157Thr did not reveal statistically significant differences; however, the observed combinations underscore the need for deeper investigation into the interplay between germline and somatic events in lung carcinogenesis. Particular attention is warranted for patients with multiple primary malignancies, consistent with the known multi-organ cancer susceptibility associated with pathogenic CHEK2 variants and emphasizing the limited representation of such patients in current NSCLC guidelines.

The practical value of the obtained data lies in their potential to inform regional approaches to genetic counseling and refine the interpretation of NGS profiles. With further data accumulation, it may become possible to determine whether germline CHEK2 variants – especially p.Ile157Thr –serve as prognostic markers, risk-stratification factors, or indirect indicators of the likelihood of specific somatic drivers.

References

1. Wild CP, Weiderpass E, Stewart BW (eds). World Cancer Report. Lyon (FR): International Agency for Research on Cancer; 2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK606998/
2. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018 Jan 24;553(7689):446–454. https://doi.org/10.1038/nature25183
3. Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. Nat Rev Cancer. 2003 Oct;3(10):733-44. https://doi.org/10.1038/nrc1190 Erratum in: Nat Rev Cancer. 2004 Jan;4(1):84.
4. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004 Jun 4;304(5676):1497–1500. https://doi.org/10.1126/science.1099314
5. Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA. 2014 May 21;311(19):1998–2006. https://doi.org/10.1001/jama.2014.3741
6. Sorscher S, LoPiccolo J, Heald B, Chen E, Bristow SL, Michalski ST, et al. Rate of Pathogenic Germline Variants in Patients With Lung Cancer. JCO Precis Oncol. 2023 Sep;7:e2300190. https://doi.org/10.1200/po.23.00190

7. Bell DW, Varley JM, Szydlo TE, Kang DH, Wahrer DC, Shannon KE, et al. Heterozygous germ line hCHK2 mutations in Li-Fraumeni syndrome. Science. 1999 Dec 24;286(5449):2528–2531. https://doi.org/10.1126/science.286.5449.2528
8. Meijers-Heijboer H, van den Ouweland A, Klijn J, Wasielewski M, de Snoo A, Oldenburg R, et al.; CHEK2-Breast Cancer Consortium. Low-penetrance susceptibility to breast cancer due to CHEK2(*)1100delC in noncarriers of BRCA1 or BRCA2 mutations. Nat Genet. 2002 May;31(1):55–59. https://doi.org/10.1038/ng879
9. Vahteristo P, Bartkova J, Eerola H, Syrjäkoski K, Ojala S, Kilpivaara O, et al. A CHEK2 genetic variant contributing to a substantial fraction of familial breast cancer. Am J Hum Genet. 2002 Aug;71(2):432–438. https://doi.org/10.1086/341943
10. Kilpivaara O, Vahteristo P, Falck J, Syrjäkoski K, Eerola H, Easton D, et al. CHEK2 variant I157T may be associated with increased breast cancer risk. Int J Cancer. 2004 Sep 10;111(4):543–547. https://doi.org/10.1002/ijc.20299
11. Cybulski C, Górski B, Huzarski T, Masojć B, Mierzejewski M, Debniak T, et al. CHEK2 is a multiorgan cancer susceptibility gene. Am J Hum Genet. 2004 Dec;75(6):1131–1135. https://doi.org/10.1086/426403
12. Weischer M, Bojesen SE, Ellervik C, Tybjaerg-Hansen A, Nordestgaard BG. CHEK2*1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. J Clin Oncol. 2008 Feb 1;26(4):542–548. https://doi.org/10.1200/jco.2007.12.5922
13. Xiang HP, Geng XP, Ge WW, Li H. Meta-analysis of CHEK2 1100delC variant and colorectal cancer susceptibility. Eur J Cancer. 2011 Nov;47(17):2546–2551. https://doi.org/10.1016/j.ejca.2011.03.025
14. Stolarova L, Kleiblova P, Janatova M, Soukupova J, Zemankova P, Macurek L, Kleibl Z. CHEK2 Germline Variants in Cancer Predisposition: Stalemate Rather than Checkmate. Cells. 2020 Dec 12;9(12):2675. https://doi.org/10.3390/cells9122675
15. Bermisheva MA, Takhirova ZR, Khusnutdinova EK, Bogdanova N. Frequency of CHEK2 gene mutations in breast cancer patients from republic of Bashkortostan. Molecular Biology. 2014;48(1):46–51. https://doi.org/10.7868/s0026898414010029
16. Kazakov AM, Laktionov KK, Sarantseva KA, Gordiev MG. Relationship between molecular genetic and clinical and morphological parameters in patients with stage I–IIIA non-small cell lung cancer. Russian Journal of Biotherapy. 2023;24(3):291–299. (In Russ.). https://doi.org/10.31917/2403291
17. Brennan P, McKay J, Moore L, Zaridze D, Mukeria A, Szeszenia-Dabrowska N, et al. Uncommon CHEK2 mis-sense variant and reduced risk of tobacco-related cancers: case control study. Hum Mol Genet. 2007 Aug 1;16(15):1794–1801. https://doi.org/10.1093/hmg/ddm127
18. Cybulski C, Masojc B, Oszutowska D, Jaworowska E, Grodzki T, Waloszczyk P, et al. Constitutional CHEK2 mutations are associated with a decreased risk of lung and laryngeal cancers. Carcinogenesis. 2008 Apr;29(4):762–765. https://doi.org/10.1093/carcin/bgn044
19. Wang Y, McKay JD, Rafnar T, Wang Z, Timofeeva MN, Broderick P, et al. Rare variants of large effect in BRCA2 and CHEK2 affect risk of lung cancer. Nat Genet. 2014 Jul;46(7):736-41. https://doi.org/10.1038/ng.3002 Epub 2014 Jun 1. Erratum in: Nat Genet. 2017 Mar 30;49(4):651. https://doi.org/10.1038/ng0417-651a
20. Kharagezov DA, Lazutin YuN, Mirzoyan EA, Milakin AG, Stateshny ON, Leiman IA, Chubaryan AV, Iozefi KD. Molecular targets of non-small cell lung cancer outside the "top three". South Russian Journal of Cancer. 2021;2(4):38–47. https://doi.org/10.37748/2686-9039-2021-2-4-5
21. Zhang SS, Lee JK, Tukachinsky H, Schrock AB, Nagasaka M, Ou SI. A High Percentage of NSCLC With Germline CHEK2 Mutation Harbors Actionable Driver Alterations: Survey of a Cancer Genomic Database and Review of Literature. JTO Clin Res Rep. 2022 Aug 6;3(9):100387. https://doi.org/10.1016/j.jtocrr.2022.100387
22. Mezquita L, Kuang Z, Sivakumar S, Sokol ES, Laguna JC, Pastor B. et al. Pathogenic Germline Variants in Patients with Non-Small Cell Lung Cancer (NSCLC) Detected by Tissue Comprehensive Genomic Profiling. Journal of Thoracic Oncology. 2023;18(S11):151. https://doi.org/10.1016/j.jtho.2023.09.217
23. Zhou N, Xu Y, Huang Y, Ye G, Luo L, Song Z. Comprehensive genomic profiling of Chinese lung cancer characterizes germline-somatic mutation interactions influencing cancer risk. J Transl Med. 2025 Feb 18;23(1):199. https://doi.org/10.1186/s12967-025-06096-z

24. Daly MB, Pal T, AlHilli Z, Arun B, Buys SS, Cheng HH, et al. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment – Breast, Ovarian, Pancreatic & Prostate; Version 3.2025. Plymouth Meeting (PA): National Comprehensive Cancer Network; 6 Mar 2025 [Дата обращения: 23 июня 2025 года].
Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf
25. Gupta S, Weiss JM, Axell L, Burke CA, Chen LM, Chung DC, et al. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment – Colorectal, Endometrial & Gastric; Version 1.2025. Plymouth Meeting (PA): National Comprehensive Cancer Network; 13 Jun 2025 [Accessed 23 June 2025].
Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf
26. Wood DE, Kazerooni EA, Aberle DR, Baines J, Boer B, Brown LM, et al. NCCN Clinical Practice Guidelines in Oncology: Lung Cancer Screening; Version 1.2025. Plymouth Meeting (PA): National Comprehensive Cancer Network; 14 Oct 2024 [Accessed 23 June 2025]. Available at: https://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf
27. Riely GJ, Wood DE, Aisner DL, Axtell AL, Bauman JR, Bharat A, et al. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer; Version 5.2025. Plymouth Meeting (PA): National Comprehensive Cancer Network; 20 Jun 2025 [Accessed 23 June 2025]. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Information about authors:

Albert M. Sigal ✉ – Cand. Sci. (Medicine), Associate Professor of the Department of Surgery, Kazan Federal University, Kazan, Russian Federation; thoracic surgeon, oncologist of the Oncology Department No. 1, The Republican Clinical Oncological Dispensary named after Prof. M.Z. Sigal, Kazan, Russian Federation
ORCID: https://orcid.org/0000-0002-5918-4225, eLibrary SPIN: 6457-2742, AuthorID: 909681

Marat G. Gordiev – Cand. Sci. (Medicine), Head of the Genetics Laboratory, Moscow Scientific and Practical Center for Laboratory Research, Moscow, Russian Federation
ORCID: https://orcid.org/0000-0002-3848-865X, eLibrary SPIN: 8388-3566, AuthorID: 847417, Scopus Author ID: 55443225000

Bulat F. Mostyukov – MD, resident physician of the Department of Oncology, Radiology and Palliative Medicine, Kazan State Medical Academy – Branch Campus of the Russian Medical Academy of Continuous Professional Education, Kazan, Russian Federation
ORCID: https://orcid.org/0009-0002-4478-0443

Natalia Z. Sattarova – resident physician in the specialty "Oncology" of the Department of Surgery of the Institute of Physiotherapy and Biomedical Sciences, Kazan Federal University, Kazan, Russian Federation
ORCID: https://orcid.org/0009-0000-9791-9619

Sergey V. Zinchenko – Dr. Sci. (Medicine), Associate Professor, Head of the Department of Surgery, Kazan Federal University, Kazan, Russian Federation
ORCID: https://orcid.org/0000-0002-9306-3507, SPIN: 5381-4389, AuthorID: 905414, Scopus Author ID: 57209135318

Contribution of the authors:

Sigal A. M. – conception and study design, investigation, scientific supervision, project administration, manuscript editing;
Gordiev M. G. – scientific consultancy (NGS-analysis design, genetic data interpretation), provision of resources (NGS data), manuscript editing;
Mostyukov B. F. – analysis and interpretation of study results, literature review, manuscript drafting, manuscript editing;
Sattarova N. Z. – investigation, data analysis, manuscript editing, organizational support;
Zinchenko S. V. – scientific consultancy; manuscript editing.
All authors made equivalent contributions to the preparation of the article and approved the final version for publication.