Received: 02 December 2024 / Accepted: 29 January 2025 / Published online: 28 February 2025

DOI 10.34689/SH.2025.27.1.019

UDC 616.441-008.63

THE IMPACT OF GENE MUTATIONS IN THYROID CANCER: A REVIEW

Akerke Kh. Yerketayeva[1], https://orcid.org/0009-0009-6010-3339
Zhanna B. Mussazhanova[2,3], https://orcid.org/0000-0002-7315-7725
Zhanna Y. Kozykenova[1], https://orcid.org/0000-0001-7420-2279
Laura A. Pak[1], https://orcid.org/0000-0002-5249-3359
Zaure D. Dushimova[2], https://orcid.org/0000-0003-0791-4246
Bakytkul Zh. Toktabayeva[1], https://orcid.org/0000-0001-5899-1247
Lashyn K. Zhazykbayeva[1], https://orcid.org/0000-0001-6529-284X
Aidana M. Rakhmankulova[1], https://orcid.org/0000-0003-3307-413X

[1] NCJSC "Semey Medical University", Semey, the Republic of Kazakhstan;
[2] Al-Farabi Kazakh National University, Almaty, the Republic of Kazakhstan;
[3] Department of Tumor and Diagnostic Pathology, Atomic Bomb Disease Institute, Nagasaki, Japan.

Abstract

Introduction: Thyroid cancer is a common endocrine malignancy, with DICER1 mutations emerging as significant contributors to its development and progression. The identification of these mutations through molecular genetic analysis, particularly in poorly differentiated thyroid carcinomas and pediatric follicular thyroid carcinomas, has provided valuable insights into the pathophysiological mechanisms underlying the disease. Studies by Volante et al. and Lee et al. have highlighted the importance of genetic testing for DICER1 mutations in guiding clinical management, enabling more precise risk stratification, and tailoring patient-specific therapeutic approaches. Despite these advances, critical gaps remain in our understanding of the full spectrum of DICER1-associated phenotypes and the molecular mechanisms involved. Future research is needed to elucidate the biological pathways influenced by DICER1 mutations and to explore the potential for targeted therapies. Additionally, developing strategies for early detection and personalized treatment plans based on genetic profiles could significantly improve patient outcomes.

This review **aims** to analyze publications devoted to the significant role of DICER1 mutations in thyroid cancer.

Search strategy: The literature search was performed in the electronic databases PubMed, WoS, Scopus, Google Scholar over the past 10 years: from 2014 to 2024, but information about topic (the Impact of DICER1 Mutations on Thyroid Cancer) was not full. Most of the valuable information related to the problem, found in the databases, was from 2005–2007, 2009, and 2011–2013, and was included in the review. These sources do not fall into the specified depth, but were accepted for analysis because they contain conceptual information. Criteria for inclusion of publications in the review: publications in full text access in Russian and English, bearing statistically confirmed conclusions. Exclusion criteria: abstracts of reports, newspaper publications, paid access articles, personal communications.

Results: This review synthesizes current insights into the mechanisms of formation of the DICER1 gene mutation. Despite these advances, there is no complete spectrum of DICER1-related phenotypes and molecular mechanisms involved in this process. Further research is needed to clarify the biological pathways affected by DICER1 mutations and explore the potential of targeted therapies. In addition, the development of early detection strategies and personalized treatment plans based on genetic profiles can significantly improve patient outcomes. This review highlights the need for continued research on DICER1 gene mutations to fully exploit their potential in improving the diagnosis, management, and treatment of thyroid cancer.

Conclusions: The presented data allow us to formulate a clinical and pathophysiological approach to the clinic and treatment of thyroid cancer. Conducting genetic analysis for DICER1 gene mutations can lead to the development of personalized and effective treatment plans. The study of DICER1 mutations will improve patient outcomes by improving the approach to the diagnosis and treatment of thyroid cancer. Thus, the detection of the presence of a DICER1 gene mutation in thyroid cancer is an important part in the management of patients with thyroid cancer, which will also improve the outcome of the disease.

Keywords*: papillary thyroid carcinoma, well-differentiated thyroid cancer, DICER1 mutation, DICER1 in thyroid tumor, DICER1 in endocrine pathology*.

For citation:

Yerketayeva A.Kh., Mussazhanova Zh.B., Kozykenova Zh.Y., Pak L.A., Dushimova Z.D., Toktabayeva B.Zh., Zhazykbayeva L.K., Rakhmankulova A.M. The Impact of gene mutations in Thyroid Cancer: A review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (1), pp. 157-166. *doi 10.34689/SH.2025.27.1.019*

Резюме

РОЛЬ МУТАЦИИ В ГЕНЕ ПРИ РАКЕ ЩИТОВИДНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ.

Акерке Х. Еркетаева[1], https://orcid.org/0009-0009-6010-3339
Жанна Б. Мусажанова[2,3], https://orcid.org/0000-0002-7315-7725
Жанна У.Козыкенова[1], https://orcid.org/0000-0001-7420-2279
Лаура А. Пак[1], https://orcid.org/0000-0002-5249-3359
Зауре Д. Душимова[2], https://orcid.org/0000-0003-0791-4246
Бакыткуль Ж. Токтабаева[1], https://orcid.org/0000-0001-5899-1247
Лашын К.Жазыкбаева[1], https://orcid.org/0000-0001-6529-284X
Айдана М. Рахманкулова[1], https://orcid.org/0000-0003-3307-413X

[1] НАО «Медицинский университет Семей», г. Семей, Республика Казахстан;
[2] Казахский национальный университет им. Аль-Фараби, г. Алматы, Республика Казахстан;
[3] Отделение диагностики патологии и опухоли, Институт заболеваний от атомных взрывов, г. Нагасаки, Япония.

Введение: Рак щитовидной железы - распространенное эндокринное злокачественное новообразование, в развитии и прогрессировании которого значительную роль играет мутация гена DICER1. Выявление этих мутаций с помощью молекулярно-генетического анализа, особенно в низко дифференцированных карциномах щитовидной железы и детских фолликулярных карциномах щитовидной железы, позволило получить ценные сведения о патофизиологических механизмах, лежащих в основе этого заболевания. Исследования Volante et al. и Lee et al. подчеркнули важность генетического тестирования на мутации DICER1 для руководства клиническим лечением, более точной стратификации риска и подбора терапевтических подходов с учетом индивидуальных особенностей пациента.

Целью данного обзора являлась систематизация данных о роли мутаций DICER1 при раке щитовидной железы.

Стратегия поиска: Поиск литературы проводился в электронных базах данных PubMed, WoS, Scopus, Google Scholar за последние 10 лет: с 2014 по 2024 год, но информация по теме (влияние мутаций DICER1 на рак щитовидной железы) была неполной. Большая часть ценной информации, описывающей проблему, найденную в базах данных за 2005–2007, 2009, 2011–2013 годы, была включена ввиду отражения основной проблемы темы. Критерии включения публикаций в обзор: публикации в полнотекстовом доступе на русском и английском языках, содержащие статистически подтвержденные выводы. Критерии исключения: тезисы докладов, газетные публикации, статьи в платном доступе, личные сообщения.

Результаты: В представленном обзоре систематизированы современные взгляды на механизмы формирования мутации гена DICER1. Несмотря на эти достижения, нет полного спектра фенотипов, связанных с DICER1, и молекулярных механизмов, вовлеченных в этот процесс. Разработка стратегий раннего выявления и персонализированных планов лечения на основе генетических профилей может значительно улучшить результаты лечения пациентов. Данный обзор подчеркивает необходимость продолжения исследований мутаций гена DICER1 для полного использования их потенциала в улучшении диагностики, ведения и лечения рака щитовидной железы.

Выводы: Представленные данные позволяют сформулировать клинико-патофизиологический подход к клинике и лечению рака щитовидной железы. Проведение генетического анализа на мутации гена DICER1 может привести к разработке персонализированных и эффективных планов лечения. Исследование мутаций DICER1 улучшат результаты лечения пациентов за счет совершенствования подхода к диагностике и лечению рака щитовидной железы. Таким образом, выявление наличия мутации гена DICER1 при раке щитовидной железы является важной частью при ведении пациентов с раком щитовидной железы, которая улучшит так же исход течения заболевания.
***Ключевые слова**: папиллярная карцинома щитовидной железы, высокодифференцированный рак щитовидной железы, мутация DICER1, DICER1 при опухоли щитовидной железы, DICER1 при эндокринной патологии.*

Для цитирования:

Еркетаева А.Х., Мусажанова Ж.Б., Козыкенова Ж.У., *Пак Л.А., Душимова З.Д., Токтабаева Б.Ж., Жазыкбаева Л.К., Рахманкулова А.М.* Роль мутации в гене при раке щитовидной железы: Обзор литературы // Наука и Здравоохранение. 2025. Vol.27 (1), С.157-166. *doi 10.34689/SH.2025.27.1.019*

Түйіндеме

ҚАЛҚАНША БЕЗІНІҢ ҚАТЕРЛІ ІСІГІНДЕГІ ГЕНІНІҢ МУТАЦИЯСЫНЫҢ РӨЛІ: ӘДЕБИЕТТІК ШОЛУ.

Акерке Еркетаева[1], https://orcid.org/0009-0009-6010-3339
Жанна Мусажанова[2,3], https://orcid.org/0000-0002-7315-7725
Жанна Козыкенова[1],https://orcid.org/0000-0001-7420-2279
Лаура Пак[1], https://orcid.org/0000-0002-5249-3359
Зауре Душимова[2], https://orcid.org/0000-0003-0791-4246
Бакыткуль Ж. Токтабаева[1], https://orcid.org/0000-0001-5899-1247
Лашын Жазыкбаева[1], https://orcid.org/0000-0001-6529-284X
Айдана Рахманкулова[1], https://orcid.org/0000-0003-3307-413X

[1] «Семей медицина университеті» КеАҚ, Семей қ., Қазақстан Республикасы;
[2] Әл-Фараби атындағы Қазақ Ұлттық университеті, Алматы қ., Қазақстан Республикасы;
[3] Патология және ісік диагностикасы бөлімі, Атомдық жарылыс аурулары институты, Нагасаки қ., Жапония:

Кіріспе; Қалқанша безінің обыры кең таралған эндокриндік қатерлі ісік болып табылады, бұл ретте DICER1 мутациялар оның дамуы мен ілгерілеуінің елеулі фактор атқарады. Бұл мутацияларды молекулалық-генетикалық талдаудың көмегімен, әсіресе қалқанша безінің нашар сараланған карциномаларында және қалқанша безінің педиатриялық фолликулярлық карциномаларында сәйкестендіру аурудың негізінде жатқан патофизиологиялық тетіктер туралы құнды ақпарат берді. Volante et al. Ли және басқалар клиникалық жүргізу, қауіптерді неғұрлым дәл стратификациялауды қамтамасыз ету және емделушіге тән терапевтік тәсілдерді бейімдеу бойынша DICER1 мутацияларына генетикалық тестілеудің маңыздылығын атап өтті. Осы жетістіктерге қарамастан, DICER1-associated фенотиптері мен тартылған молекулалық механизмдердің толық спектрін түсінуде сыни олқылықтар бар. Болашақ зерттеулер DICER1 мутациялар әсер ететін биологиялық жолдарды анықтау үшін және мақсатты бағытталған терапияның әлеуетін зерттеу үшін қажет. Бұдан басқа, генетикалық бейіндер негізінде ерте анықтау стратегиялары мен дербестендірілген емдеу жоспарларын әзірлеу пациенттерді емдеу нәтижелерін айтарлықтай жақсартуы мүмкін. Бұл шолуда қалқанша безі обырын диагностикалауды, емдеуді және емдеуді жақсарту үшін олардың әлеуетін толық пайдалану үшін DICER1 мутацияларын зерттеуді жалғастыру қажеттігі атап өтіледі.

Бұл шолудың мақсаты: қалқанша безінің қатерлі ісігіндегі DICER1 мутацияларының рөлі туралы деректерді жүйелеу.

Іздеу стратегиясы: маңызды әдебиеттерді ізденіс PubMed, Web of Science дерекқорларынан және электронды дерекқорларында жүргізілді: 2014 жылдан 2024 жылға дейін, бірақ тақырып бойынша ақпарат (DICER1 мутациясының қалқанша безінің қатерлі ісігіне әсері) толық болмады. 2005-2007, 2009, 2011-2013 жылдардағы мәліметтер базасында табылған мәселені сипаттайтын құнды ақпараттың көп бөлігі танысу үшін енгізілген. Бұл көздер көрсетілген тереңдікке сәйкес келмейді, бірақ талдау үшін қабылданды, өйткені олар тұжырымдамалық ақпаратты қамтиды. Басылымдарды шолуға қосу критерийлері: статистикалық расталған қорытындыларды қамтитын орыс және ағылшын тілдеріндегі толық мәтінді қол жетімділіктегі басылымдар. Ерекшелік критерийлері: баяндамалар тезистері, газет басылымдары, ақылы мақалалар, жеке хабарламалар.

Нәтижесі: Ұсынылған шолуда DICER1 генінің мутациясын қалыптастыру механизмдері туралы заманауи көзқарастар жүйеленген. Осы жетістіктерге қарамастан, DICER1-мен байланысты фенотиптердің толық спектрі және процеске қатысатын молекулалық механизмдер жоқ. DICER1 мутациялары әсер ететін биологиялық жолдарды анықтау және мақсатты терапияның әлеуетін зерттеу үшін қосымша зерттеулер қажет. Сонымен қатар, ерте анықтау стратегияларын және генетикалық профильдерге негізделген жекелендірілген емдеу жоспарларын әзірлеу пациенттердің нәтижелерін айтарлықтай жақсарта алады. Бұл шолу қалқанша безінің қатерлі ісігін диагностикалауды, басқаруды және емдеуді жақсартуда олардың әлеуетін толық пайдалану үшін DICER1 генінің мутацияларын зерттеуді жалғастыру қажеттілігін көрсетеді.

Қорытынды: Ұсынылған деректер клиникаға және қалқанша безінің қатерлі ісігін емдеуге клиникалық-патофизиологиялық тәсілді тұжырымдауға мүмкіндік береді. DICER1 генінің мутациясына генетикалық талдау жүргізу жекелендірілген және тиімді емдеу жоспарларын жасауға әкелуі мүмкін. DICER1 мутациясын зерттеу қалқанша безінің қатерлі ісігін диагностикалау және емдеу тәсілін жақсарту арқылы пациенттердің нәтижелерін жақсартады. Осылайша, қалқанша безінің қатерлі ісігінде DICER1 генінің мутациясының болуын анықтау қалқанша безінің қатерлі ісігі бар науқастарды басқарудың маңызды бөлігі болып табылады, бұл аурудың ағымының нәтижесін жақсартады.

Түйінді сөздер: *қалқанша безінің папиллярлы карциномасы, қалқанша безінің жоғары сараланған қатерлі ісігі, DICER1 мутациясы, қалқанша безінің ісігіндегі DICER1, эндокриндік патологиядағы DICER1.*

Дәйексөз үшін: Еркетаева *А.Х., Мусажанова Ж.Б., Козыкенова Ж.У., Пак Л.А., Душимова З.Д., Токтабаева Б.Ж., Жазыкбаева Л.К., Рахманкулова А.М.* Қалқанша безінің қатерлі ісігіндегі генінің мутациясының рөлі. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (1), Б. 157-166. *doi 10.34689/SH.2025.27.1.019*

Introduction

Thyroid carcinoma one of the most prevalent malignancy among adolescent and young adult females, with its incidence steadily rising across all age demographics, as evidenced in various epidemiological studies [37, 47]. Concurrently, nodular thyroid disease is notably prevalent within the adolescent population, with the widespread adoption of cervical ultrasonography revealing an increasing number of previously subclinical thyroid nodules.

The presentation of thyroid carcinoma in pediatric and adolescent cohorts exhibits several distinctive clinical characteristics when contrasted with the adult population.

Notably, these younger patients demonstrate a significantly higher propensity for both regional and distant metastasis at the time of diagnosis. Moreover, recurrence rates are disproportionately elevated in this demographic compared to their adult counterparts 72]. Intriguingly, despite the more substantial initial disease burden, prognostic outcomes for children and adolescents with thyroid carcinoma remain exceptionally favorable [60]. Furthermore, certain histopathological subtypes of papillary thyroid carcinoma (PTC), such as the diffuse sclerosing and solid variants, are more frequently encountered in pediatric and adolescent patients than in adults [32, 38]. However, the underlying biological and molecular mechanisms that contribute to the divergent clinical behavior of pediatric versus adult PTC remain poorly understood and have yet to be elucidated in the current scientific literature.

According to the literature, the probability of recurrence of thyroid cancer in children after primary surgical treatment depends on the morphological structure of the tumor and ranges from 7 to 47%. The study of the molecular mechanisms of these tumors is becoming extremely relevant, providing the opportunity to improve diagnosis, prognosis, and the future development of new targeted chemotherapeutic agents.

Thyroid cancer arise from the follicular epithelial cells or parafollicular C cells. The most common neoplasms arising from follicular cells with 4 histological types are papillary thyroid carcinomas (PTC; 80-85%), follicular thyroid cancers (FTC; 10-15%), poorly differentiated thyroid cancer (PDTC; less than 2%), and anaplastic thyroid cancer (ATC; less than 2%). PTC and FTC are termed well-differentiated thyroid cancer (WDTC), the commonest in thyroid tumor cases. The genetic landscape of differentiated thyroid cancer comprises alterations, such as BRAF and RAS mutations, and RET/PTC rearrangements, which in turn converge to activate the MAPK oncogenic pathway [72, 60]. The notion that advanced tumors dedifferentiate from WDTC towards PDTC or ATC, as is suggested by the existence of both differentiated and anaplastic foci within undifferentiated tumors, is experienced. Of particular importance is the presence of the BRAFV600E mutation or RAS mutation in about 23% and 20% of the cases of ATC, respectively. However, other mutations, such as TP53 and TERT promoter ones, along with these earlier mentioned driver mutations, are more often found in ATC [32, 42]. It is thus postulated that this accumulation of additional pathogenic alterations within oncogenes and tumor suppressor genes is a key driver of the advancement from WDTC towards PDTC and ATC.

In addition to these well-characterized mutations, emerging evidence highlights the role of DICER1 mutations in thyroid carcinogenesis. DICER1, an essential enzyme in microRNA (miRNA) processing, plays a critical role in gene regulation [2]. Mutations in DICER1 have been identified in various types of thyroid cancer, particularly in FTC and PDTC, where they contribute to the dysregulation of miRNA processing and subsequent aberrant gene expression [21, 49]. Patients harboring DICER1 mutations often present with more aggressive disease phenotypes and poorer clinical outcomes, and these mutations have been associated with familial thyroid cancer syndromes [28, 56]. Ongoing research continues to explore the interaction of DICER1 mutations with other genetic alterations, such as BRAF and RAS mutations, further elucidating their role in thyroid cancer progression [41, 51].

PTC, the most prevalent form of thyroid cancer, constitutes over 80% of all thyroid malignancies [9]. The rising incidence of thyroid cancer is largely attributed to increased diagnoses of small PTCs, which, although generally indolent and highly curable, exhibit a significant recurrence rate—about 20% at 10 years and 30% at 30 years post-treatment [43, 62]. This recurrence can have profound psychosocial and economic impacts, diminishing the quality of life for patients.

Despite the overall low mortality associated with thyroid cancer, standard treatments—such as surgical resection combined with radioiodine ablation therapy—are highly effective for most patients [8]. However, an increased risk of mortality exists when the cancer becomes surgically inoperable or loses its ability to take up radioiodine [66]. Currently, the mortality rate for thyroid cancer in the United States stands at approximately 1,530 cases per year [59]. Consequently, accurate risk stratification and prognostic evaluation are critical in managing patients and reducing both recurrence and mortality rates associated with thyroid cancer [48].

Search strategy. The literature search was performed in the electronic databases PubMed, WoS, Scopus, Google Scholar over the past 10 years: from 2014 to 2024, but information about the topic (the Impact of DICER1 Mutations on Thyroid Cancer) was not full. Most of valuable information which is described the problem founded in databases were from 2005-2007, 2009, 2011-2013, they were included to review. These sources do not fall into the specified depth, but were accepted for analysis because they contain conceptual information. *Criteria for inclusion* of publications in the review: publications in full text access in Russian and English, bearing statistically confirmed conclusions. *Exclusion criteria*: abstracts of reports, newspaper publications, paid access articles, personal communications. From the remaining articles, a plan was formed to write a literature review according to the following sequence: «DICER 1 gene mutations», «DICER1 mutations on thyroid cancer», «Molecular genetic alterations in thyroid cancer». The search was performed by keywords like "well differentiated thyroid cancer," "DICER1 endocrine pathology". According to the topic, depth of research, and keywords, 94 articles were found, of which 73 were selected for review. The source selection algorithm is presented in Figure 1.

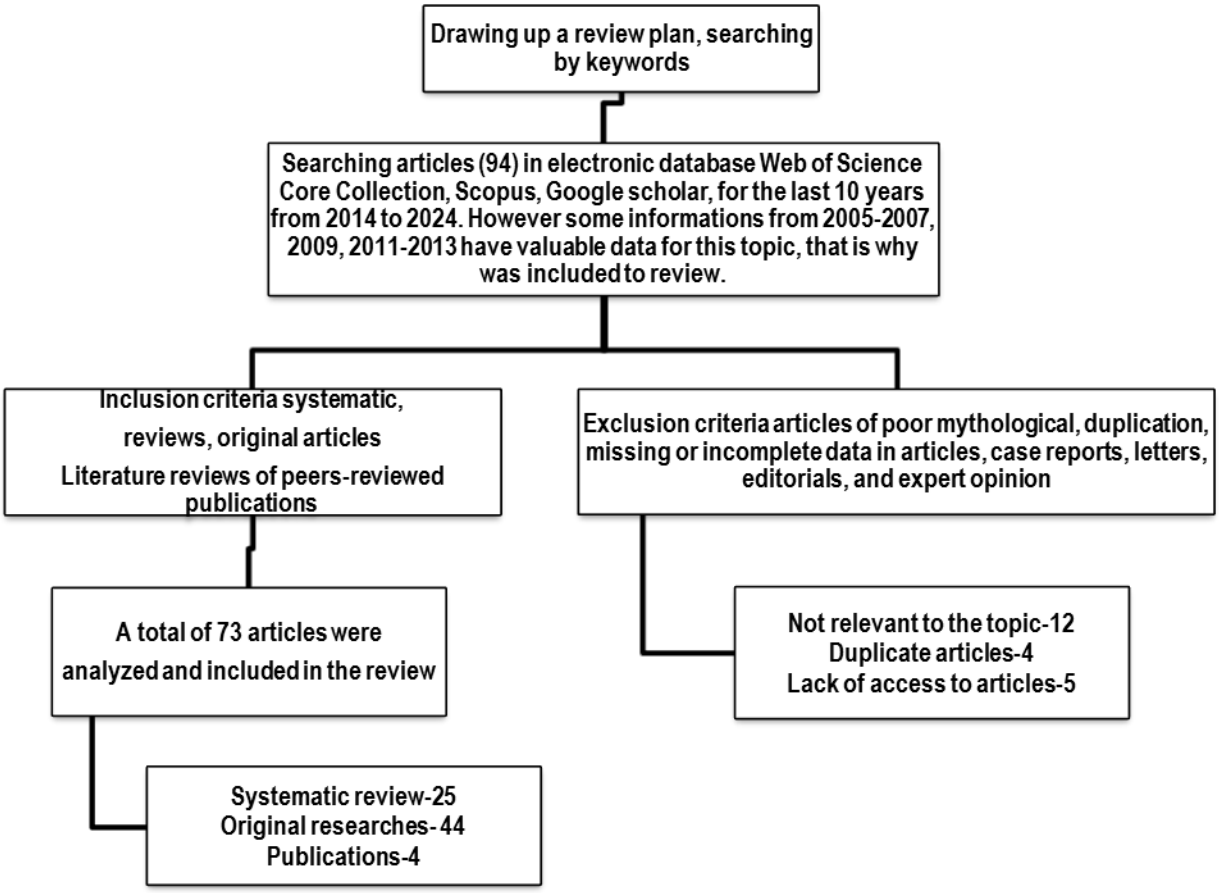

Figure 1. Article selection algorithm.

DICER1 Mutation and Its Role in Endocrine Tumors

The thyroid gland is the least studied of tumors with respect to mutations in DICER1 because, although tumors of the thyroid are the most common among the endocrine glands. The DICER1 gene, which is important for the maturation of microRNAs (miRNAs) has undergone serious work on endocrine tumors such as thyroid neoplasia. DICER1 is localized on the long arm of chromosome 14(14q32.13) and has 36 exons. Interest in DICER and its encoding protein has steadily increased in light of miRNA research, a class of short non-coding RNA molecules of roughly 22 nucleotides in length originally discovered by Ambros V. in 1993. MicroRNAs inhibit gene expression negatively at the post-transcriptional level and are involved in various biological processes such as cell proliferation and apoptosis [42].

At present, in the world literature, there is no reliable data on the impact of inactivating mutations of the DICER1 gene on the development of malignant tumors of the thyroid. Some authors have proposed that exposure to previous chemotherapy may be one of the possible factors that contribute to differentiated thyroid cancer development in such patients [2]. Other researchers suggested that DICER1 promotes thyrocyte proliferation. DICER1 mutations can actually correlate with well-differentiated thyroid carcinoma. Moreover, DICER1 protein is downregulated in papillary thyroid carcinomas, and basal expression of DICER1 is crucial for thyroid differentiation. Currently, at least two heterozygous germ-line mutations mapping to exons 8 or 25 of the DICER1 gene have been reported in patients with PTC. PTC was described in a family with papillary thyroid cancer: in a mother and her two daughters aged 12 and 14 years [4-7, 11, 21]. Michael Solarski presents an overview illustrating how mutations in DICER1 impair normal miRNA biogenesis, thereby significantly modifying gene expression. These disturbances have considerable influences on cell proliferation and differentiation, which constitute critical processes in the determination of the inception and progression of thyroid tumors. In fact, the consequence of DICER1 mutations on thyroid cancer appears particularly significant within the full spectrum of tumors, prominently FTC and PDTC, whereby aberrations in miRNA processing may promote tumor aggressiveness. In this malignancy, by modulating the aggressiveness of the tumors, DICER1 mutations could lead to the occurrence of more aggressive phenotypes, generally with poor clinical outcomes. Furthermore, mutations could also influence a tumor's response to the therapy, providing crucial opportunities for targeted treatment. For example, the extent to which normal miRNA processing is restored could render DICER1 mutant forms of thyroid cancers less aggressive. It may also open up options for targeted treatments.

Furthermore, Michael Solarski emphasizes the importance of DICER1 in the broader context of endocrine tumors, noting that the gene’s role extends beyond thyroid cancer to include other endocrine-related malignancies. The review also discusses how DICER1 mutations, when present alongside other genetic alterations such as BRAF or RAS mutations, may exacerbate tumorigenesis and

contribute to resistance to conventional therapies. This interaction highlights the complexity of genetic and epigenetic factors in thyroid cancer progression. Given these findings, DICER1 mutations could serve as both a prognostic marker and a potential therapeutic target in thyroid cancer. Understanding the specific mechanisms by which DICER1 mutations drive thyroid cancer progression remains a critical area of ongoing research. The insights from Michael Solarski underscore the need for further studies to explore how restoring miRNA processing in DICER1-mutant tumors could lead to improved treatment outcomes. Additionally, the potential for personalized treatment strategies that specifically target the molecular consequences of DICER1 mutations is an exciting area of therapeutic development. This review aims to analyze publications devoted to the significant role of DICER1 mutations in thyroid cancer, further elucidating their implications for recurrence, diagnosis, and personalized treatment strategies. [46]

DICER1 Syndrome and Thyroid Cancer

DICER1 syndrome is a hereditary condition characterized by a predisposition to various neoplasms, including thyroid cancer. De Kock L. emphasizes that pathogenic variants of DICER1 are linked to a broad spectrum of tumors, with significant implications for the thyroid gland. The study by De Kock L. provides valuable insights into how these genetic mutations contribute to thyroid cancer development, particularly in individuals with a familial history of the disease. DICER1 syndrome offers a unique framework for understanding the inherited patterns of thyroid cancer, which can differ significantly from sporadic cases.

One of the key findings in De Kock L. is the importance of early genetic testing for individuals with a family history of DICER1-related tumors. Identifying these pathogenic variants early on can lead to more effective monitoring and management strategies, potentially reducing the risk of aggressive thyroid cancer. The study also highlights how DICER1 mutations may affect the therapeutic responses in thyroid cancer patients, particularly those with hereditary cancer syndromes. Understanding these variations is crucial for developing personalized treatment plans that account for the genetic background of the patient.

De Kock L. also discusses the broader implications of DICER1 mutations beyond thyroid cancer, noting that these mutations are linked to a variety of endocrine and non-endocrine tumors. This broad spectrum of associated neoplasms underscores the complexity of DICER1 syndrome and the need for a multidisciplinary approach to patient care. The research points to the potential benefits of integrating genetic counseling into routine clinical practice for patients at risk of DICER1-related cancers. Moreover, Kock et al. suggest that further studies are needed to explore the long-term outcomes of individuals with DICER1 mutations, particularly regarding their risk for developing multiple types of cancer over their lifetime.

The findings of De Kock L. underscor the critical role of DICER1 in both the development and progression of thyroid cancer. This study contributes to the growing body of evidence that highlights the importance of genetic factors in cancer biology. As such, the insights from this research may lead to improved screening protocols and more targeted therapeutic interventions for patients with DICER1 syndrome. This review aims to analyze publications focused on the significant role of DICER1 mutations in thyroid cancer, further elucidating their implications for recurrence, diagnosis, and personalized treatment strategies. [10, 12-15] DICER1 is now accepted as a driver of pediatric thyroid nodules. Research has demonstrated an association between DICER1 somatic or germline mutations and pediatric follicular thyroid carcinoma. Can be low-risk malignancies in papillary thyroid carcinoma associate with DICER1-mutation. Some researchers approved that poorly differentiated thyroid carcinomas (PDTC) in pediatric patients are associated with DICER1 mutations, and some may be part of a DICER1 tumor syndrome. PDTC of childhood and adolescence is very rare and information is limited. Findings of some authors indicate that pediatric DICER1 mutation genetically different from adult PDTC that is strongly associated with DICER1 mutations. [12] Medullary thyroid cancer (MTC) in children poses the necessity to rule out multiple endocrine neoplasia syndrome (MEN type 2). It's noteworthy that familial cases of follicular cell-derived tumors, aside from MTC, are uncommon. Exploring the role of microRNAs as potential biomarkers in pediatric thyroid carcinomas is an emerging area of research, and expanding our understanding in this realm could pave the way for more nuanced diagnostic approaches and tailored treatments in pediatric thyroid cancer DICER 1 gene expression associated with aggressive features in patients with PTC, while with DICER1 syndrome associated DTC, which is mostly define in patients young age, and form low risk group with low probability for metastasis. [1-7, 11, 51].

Prevalence and Diagnosis of Implications for Clinical Practice

The identification of DICER1 mutations provided by molecular genetic analysis, such as next-generation sequencing, which is plays a crucial role in the clinical management of thyroid cancer, particularly in cases with poorly differentiated features. Volante et al. conducted a clinicopathologic study of 183 patients with poorly differentiated thyroid carcinomas characterized by trabecular, insular, and solid patterns, highlighting the aggressive nature of these tumors. The study underscored the importance of accurate histopathologic assessment in conjunction with genetic testing to better understand the prognosis and potential for recurrence in thyroid cancer patients.[68, 18-19]

Lee et al. further emphasized the significance of DICER1 mutations, particularly in pediatric follicular thyroid carcinomas, where these mutations are predominant. The identification of these pathogenic variants is paramount for assessing the risk of differentiated thyroid cancer recurrence, particularly in younger patients. The genetic insights provided by these studies are crucial for tailoring patient-specific therapeutic approaches, which can significantly improve clinical outcomes.[20-24]

In clinical practice, integrating genetic testing for DICER1 mutations into the diagnostic and treatment planning process allows for more precise risk stratification. For instance, patients with DICER1 mutations may require more intensive monitoring and potentially more aggressive treatment to mitigate the higher risk of recurrence and progression. Volante et al.

highlighted the need for early and accurate identification of poorly differentiated thyroid carcinomas, which can inform the choice of therapeutic strategies and improve survival rates. [25-27, 30, 31, 39, 68]

Molecular genetic analysis with next generation sequencing (NGS) narrowed down (for the particular family) the association of PTC with germline DICER1 mutations in the family under consideration. An experiment with a knock-in mice model validated these studies and clearly demonstrated that the thyroid condition occurred mainly through the knockout of Dicer1 in thyroid cells. According to new studies, some cell types have been shown to carry low levels of DICER1 and high levels of the associated proteins suggested to play a role in the development of thyroid cancer. Nevertheless, as indicated by one study, such cells when combined with environmental agents got transformed into a disorganized state that is typical of cancer tissue, before manifesting the pure cancer phenotype. Likewise, actually the role of DICER1 in cancer is dual: the mutation either enhances the protein or reduces its phosphopeptides. This occurs through the VAV1 kinase regulated DICER1 as it phosphorylates at a tyrosine residue to form a phosphopeptide that reduces the cis-modifications. NGS-based cancer gene panels can be included in childhood patients with different genetic syndromes to accurately detect the patient's disease and also to prevent cancer diseases from developing. The clinical management that includes a genetic cancer test remains the perfect course of action to take as among other things, the patient receives a clear prognosis and also, the risk predispositions are additionally understood. Children who undergo genetic tests and periodic tests might have a higher chance of resolving DNA issues and thus they will show a reduced amount of cancer diseases and more of those cases that appear will have a clear predisposing genetic factor [31,33-36, 40]

The next generation sequencing and other advanced molecular procedures in the clinical setting leads to diagnosing DICER1 mutations at early stages which is especially the case for pediatric patients. On this note. as per observations of Lee et al., they have suggested that short inhibitory RNA molecules can be designed specifically for the targets as they have a particular inferable transcript complex with the RNA molecule. Also, the RNAi technology when used in therapy cells is better than in the usual cells; RNAi technology is being developed for gene silencing as a radiation-free treatment technology. [63-67] Besides, the things that have to be kept in mind are: the regular patient monitoring of those with DICER1 mutations and the prompt detection of the recurrence or the progression of the disease through active intervention.

The clinical studies of Volante et al., for example and Lee et al. As also noted by Lee et al., Volante et al., the management of thyroid cancer is a multidisciplinary challenge that should consider both histopathologic and genetic data to aid treatment decisions. Clinical implications are considerable as they allow for tailored, patient-centered care in patients with thyroid cancer. This strategy elevates the odds of getting the best, and highest quality care while at the same time minimizing overtreatment in patients with very low-risk profiles. [53-58, 61] Second, genetic testing as part of a clinical trial offers patients with an increased risk to thyroid cancer (DICER1 mutation) the best possibility in counseling and the management of their mutation carrier status. Exploiting genetic findings to individualize therapy is an important advance in oncology that facilitates target-based, yet minimally invasive strategies for chemotherapy. Conclusion: Molecular genetic analysis is essential to improve thyroid cancer diagnosis and therapy, and DICER1 mutations should be assessed [39,68,69,71]

Conclusion

The literature on DICER1 mutations underscores their significant impact on the development and progression of thyroid cancer. Basic- molecular alterations provide clues to pathophysiologic basis providing new distinguishing points of prospective clinical management as well as therapeutics. Nevertheless, despite the advances made, substantial ignorance of DICER1-associated phenotypes and molecular mechanisms still exists. In-depth exploration of the role of DICER1 in thyroid cancer will still demand rigorous and targeted research. Here is the suggested functional link of mutation gene DICER 1 active state of cancer approved with this review. Molecular genetic studies with NGS will allow one to deduce an unequivocal link between PTC and a DICER1 defect, by which can be defined both risk of malignant activation, type-of Mutations and recurrents, available; of treating disease in patient based on which treatment. Future work should focus on distinguishing affected biological pathways due to DICER1 mutations and defining a window to develop targeted therapies. Furthermore, the development of candidate molecular tests for identifying patient sub-populations in which genetic profiles could be useful may facilitate more personalized and effective treatment regimes. Also, these data suggest a primary driver of oncogenic activation for the DICER1 in pediatric low-risk PTCs pushed the molecular pathogenesis of PTCs. Future studies of DICER1 mutations are likely to lead to improved management practices for thyroid cancer diagnosis and treatment in patients. To sum up: DICER1 in thyroid cancer is an urgent field to address studies that can have a substantial impact on patient outcome.

Conflict of Interest

The authors declare no conflicts of interest. Additionally, no part of this article has been previously published or is under consideration by other publishers.

Author Contributions

As this is a review article, all authors contributed to the literature search using separate methodologies, and the decision to exclude certain materials was made collectively.

Funding

This study was funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP19680262: "Clinical and epidemiological characterization of risk factors for osteoporosis prevalence across different age groups, with an assessment of bone tissue composition using dual-energy X-ray absorptiometry").

References:

1. *Apellaniz-Ruiz M., de Kock, L., Sabbaghian N., Guaraldi F., Ghizzoni L., Beccuti G., Foulkes, W.D. Familial* multinodular goiter and Sertoli-Leydig cell tumors associated with a large intragenic in-frame DICER1 deletion. European Journal of Endocrinology, 2018. 178(2), K11–K19. https://doi.org/10.1530/EJE-17-0904.

2. *Bahubeshi A., Bal N., Rio Frio T.* DICER1 mutations in a broad range of follicular cell-derived thyroid cancers: Genetic and clinical implications. J Clin Endocrinol Metab, 2011. 96(9).

3. *Blokzijl F., de Ligt J., Jager M., Sasselli V., Roerink S., Sasaki N., van Boxtel R.* Tissue-specific mutation accumulation in human adult stem cells during life. Nature, 2016. 538 (7624), 260–264. https://doi.org/10.1038/nature19768.

4. *Brenneman M., Field A., Yang J., Williams G., Doros L., Rossi C., Hill .A.* Temporal order of RNase IIIb and loss-of-function mutations during development determines phenotype in pleuropulmonary blastoma/DICER1 syndrome: A unique variant of the two-hit tumor suppression model. F1000 Research, 2015. 214. https://doi.org/10.12688/f1000research.

5. *Burger K., Gullerova M. Swiss* army knives: Non-canonical functions of nuclear Drosha and Dicer. Nature Re s Molecular Cell Biology, 2015.16(7), 417–430. https://doi.org/10.1038/nrm3994.

6. *Chen J., Wang Y., Monechy M.K., Anglesio M.S., Yang W., Senz J., Huntsman D.G.* Recurrent DICER1 hotspot mutations in endometrial tumours and their impact on microRNA biogenesis. Journal of Pathology, 2015. 237(2), 215–225. https://doi.org/10.1002/path.4569.

7. *Consoli C., Moss C., Green S., Balderson D., Cooper D.N., Upadhyaya M.* Gonosomal mosaicism for a nonsense mutation (R1947X) in the NF1 gene in segmental neurofibromatosis type 1. Journal of Investigative Dermatology, 2005. 125(3), 463–466. https://doi.org/10.1111/j.0022-202X.2005.23834.x.

8. *Cooper D.S., Doherty G.M., Haugen B.R.* Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer." Thyroid, 2009. 19(11):1167-1214.

9. *Davies L., Welch H.G.* Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA, 2006. 295(18):2164-2167.

10. *De Kock L., Wu V.R., Foulkes W.D.* Ten years of DICER1 mutations: Provelance, distribution and associated phenotypes. Hum Mutant, 2019; 40(11) 1939-53.

11. *De Kock L., Geoffrion, D., Rivera, B., Wagener, R., Sabbaghian, N., Bens, S., Foulkes, W.D. Multiple* DICER1-related tumors in a child with a large interstitial 14q32 deletion. Genes, Chromosomes Cancer, 2018. 57(5), 223–230. https://doi.org/10.1002/gcc.22523.

12. *De Kock L., Hillmer M., Wagener R., Soglio D. B., Sabbaghian N., Siebert R., Foulkes W.D. Further* evidence that full gene deletions of DICER1 predispose to DICER1 syndrome. Genes Chromosomes Cancer, 2019. 58(8), 602–604. https://doi.org/10.1002/gcc.22728.

13. *De Kock L., Priest J.R., Foulkes W.D., Alexandrescu S.* An update on the central nervous system manifestations of DICER1 syndrome. Acta Neuropathologica, 2019. https://doi.org/10.1007/s00401-019-01997-y.

14. *De Kock L., Rivera B., Revil T., Thorner P., Goudie C., Bouron-Dal Soglio D., Foulkes W.D.* Sequencing of DICER1 in sarcomas identifies biallelic somatic DICER1 mutations in an adult-onset embryonal rhabdomyosarcoma. British Journal of Cancer, 2017. 116 (12), 1621–1626. https://doi.org/10.1038/bjc.2017.147.

15. *De Kock L., Sabbaghian N., Druker H., Weber E., Hamel N., Miller S., Foulkes W.D.* Germ-line and somatic DICER1 mutations in pineoblastoma. Acta Neuropathologica, 2014. 128(4), 583–595. https://doi.org/10.1007/s00401-014-1318-7.

16. *De Kock L., Terzic T., McCluggage W.G., Stewart C. J.R., Shaw P., Foulkes, W.D., Clarke, B.A.* DICER1 mutations are consistently present in moderately and poorly differentiated Sertoli-Leydig cell tumors. The American Journal of Surgical Pathology, 2017. 41(9), 1178–1187. https://doi.org/10.1097/PAS.0000000000000895.

17. *De Kock Ldo., Wang Y.C., Revil T., Badescu D., Rivera B., Sabbaghian N., Foulkes W.D.* High-sensitivity sequencing reveals multi-organ somatic mosaicism causing DICER1 syndrome. Journal of Medical Genetics, 2016. 53(1), 43–52. https://doi.org/10.1136/jmedgenet-2015-103428.

18. *Domchek S.M., Tang J., Stopfer J., Lilli D.R., Hamel N., Tischkowitz M., Greenberg R.A. Biallelic* deleterious BRCA1 mutations in a woman with early-onset ovarian cancer. Cancer Discovery, 2013. 3(4), 399–405. https://doi.org/10.1158/2159-8290.Cd-12-0421.

19. *Evans, D. R.* Neurofibromatosis type 2 (NF2): A clinical and molecular re. Orphanet Journal of Rare Diseases, 2009. 4, 16. https://doi.org/10.1186/1750-1172-4-16.

20. *Findlay G.M., Daza R.M., Martin B., Zhang M.D., Leith A.P., Gasperini M., Shendure, J. Accurate* classification of BRCA1 variants with saturation genome editing. Nature, 2018. 562(7726), 217–222. https://doi.org/10.1038/s41586-018-0461-z.

21. *Foulkes W.D., Priest J.R., Duchaine T.F.* DICER1: Mutations, microRNAs and mechanisms. Nat Rev Cancer, 2014. 14(10):662-672.

22. *Foulkes W.D., Gore M., Cluggage W.G.* Rare non-epithelial ovarian neoplasms: Pathology, genetics and treatment. Gynecologic Oncology, 2016. 142, 190–198. https://doi.org/10.1016/j.ygyno.2016.04.005.

23. *Foulkes W. D., Priest, J. R., Duchaine T. F.* DICER1: Mutations, microRNAs and mechanisms. Nature Re s Cancer, 2014. 14(10), 662–672. https://doi.org/10.1038/nrc3802.

24. *Gurtan A.M., Lu, V., Bhutkar A., Sharp P.A.* In vivo structure-function analysis of human Dicer reveals directional processing of precursor miRNAs. RNA, 2012. 18(6), 1116–1122. https://doi.org/10.1261/rna.032680.112.

25. *Heravi-Moussavi A., Anglesio M.S., Cheng S.W. G., Senz J., Yang W., Prentice L., Huntsman D. G.* Recurrent somatic DICER1 mutations in nonepithelial ovarian cancers. New England Journal of Medicine, 2012. 366(3), 234–242. https://doi.org/10.1056/NEJMoa1102903.

26. *Herriges J.C., Brown S., Longhurst M., Ozmore J., Moeschler J.B., Janze A., Andersen E.F.* Identification of two 14q32 deletions involving DICER1 associated with the development of DICER1-related tumors. European Journal of Medical Genetics, 2019. 62, 9–14. https://doi.org/10.1016/j.ejmg.2018.04.011.

27. *Hes F.J., Nielsen M., Bik E.C., Konvalinka D., Wijnen J.T., Bakker E., Tops C.M.J. Somatic APC* mosaicism: An underestimated cause of polyposis coli. Gut, 2007. 57(1), 71–76. https://doi.org/10.1136/gut.2006.117796.

28. *Hill D.A., Ivanovich J., Priest J.R.* DICER1 mutations in familial thyroid cancer: Clinical and molecular features. Thyroid, 2011. 21(10):1233-1241.

29. *Hill D.A., Ivanovich J., Priest J.R., Gurnett C. A., Dehner L.P., Desruisseau D., Goodfellow P.J.* DICER1 mutations in familial pleuropulmonary blastoma. Science, 2009. 325(5943), 965. https://doi.org/10.1126/science.1174334

30. *Hu W., Coller J.* What comes first: Translational repression or mRNA degradation? The deepening mystery of microRNA function. Cell Research, 2012. 22(9), 1322–1324. https://doi.org/10.1038/cr.2012.80.

31. *Huryn L.A., Turriff A., Harney L.A., Carr A.G., Chevez-Barrios P., Gombos D.S., Stewart, D.R.* DICER1 syndrome. Ophthalmology, 2019. 126, 296–304. https://doi.org/10.1016/j.ophtha.2018.09.038.

32. *Ibrahimpasic T, Xu B., Landa I.* Genomic alterations in fatal forms of non-anaplastic thyroid cancer: Identification of MED12 and FGF3/4 amplifications as candidate drivers. Sci Rep, 2015. 5:11332.

33. *Khan N.E., Bauer A.J., Doros, L., Schultz K.A.P., Decastro R.M., Harney, L.A., Stewart, D. R.* Macrocephaly associated with the DICER1 syndrome. Genetics in Medicine, 2016. 19, 244–248. https://doi.org/10.1038/gim.2016.83.

34. *Khan N.E., Lin, A., Raske M.E., Harney L.A., Carr A.G., Field A., Stewart D.R.* Structural renal abnormalities in the DICER1 syndrome: A family-based cohort study. Pediatric Nephrology, 2018. 33(12), 2281–2288. https://doi.org/10.1007/s00467-018-4040-1.

35. *Kim J., Field A., Schultz K.A.P., Hill D.A., Stewart D.R.* The prevalence of DICER1 pathogenic variation in population databases. International Journal of Cancer, 2017. 141(10), 2030–2036. https://doi.org/10.1002/ijc.30907.

36. *Klein S., Lee H., Ghahremani S., Kempert P., Ischander M., et al.* Expanding the phenotype of mutations in DICER1: Mosaic missense mutations in the RNase IIIb domain of DICER1 cause GLOW syndrome. Journal of Medical Genetics, 2014. 51(5), 294–302. https://doi.org/10.1136/jmedgenet-2013-101943.

37. *Kondo T., Ezzat S., Asa S.L.* Pathogenetic mechanisms in thyroid follicular-cell neoplasia. Nat Rev Cancer, 2006. 6(4):292-306.

38. *Landa I., Ganly I., Chan T.A.* "Frequent somatic TERT promoter mutations in thyroid cancer: Higher prevalence in advanced forms of the disease." J Clin Endocrinol Metab, 2013. 98(9).

39. *Lee Y.A.* Predominant DICER1 pathogenic variants in pediatric follicular thyroid carcinomas. Thyroid, 2020. 30:1120–1131.

40. *Lee J.C., Mazor T., Lao R., Wan E., Diallo A.B., Hill N.S., Solomon D.A.* Recurrent KBTBD4 small in-frame insertions and absence of DROSHA deletion or DICER1 mutation differentiate pineal parenchymal tumor of intermediate differentiation (PPTID) from pineoblastoma. Acta Neuropathologica, 2019. 137, 851–854. https://doi.org/10.1007/s00401-019-01990-5.

41. *Lu H., He Y., Lin L.* "DICER1 gene mutations in thyroid carcinoma and their association with BRAF V600E mutation and microRNA expression profiles." Cancer Genet Cytogenet, 2010. 203(3):204-208.

42. *Mao T.L., Yu J.S., Wu C.H.* The role of RAS mutations in thyroid follicular neoplasia and the effect of RET/PTC and PAX8/PPARγ on RAS-induced growth suppression. Oncogene, 2014. 33(38):4873-4880.

43. *Mazzaferri E.L.* Management of low-risk differentiated thyroid cancer. Endocr Pract, 2007. 13(5):498-512.

44. *Messinger Y.H., Stewart D.R., Priest J.R., Williams G.M., Harris A.K., Schultz K.A.P., Dehner L. P.* Pleuropulmonary blastoma: A report on 350 central pathology-confirmed pleuropulmonary blastoma cases by the International Pleuropulmonary Blastoma Registry. Cancer, 2015. 121(2), 276–285. https://doi.org/10.1002/cncr.29032 .

45. *Miao D., Margolis C.A., Vokes N.I., Liu, D., Taylor-Weiner A., Wankowicz S.M., Van Allen E.M.* Genomic correlates of response to immune checkpoint blockade in microsatellite-stable solid tumors. Nature Genetics, 2018. 50(9), 1271–1281. https://doi.org/10.1038/s41588-018-0200-2.

46. *Michael Solarski, Fabio Rotondo, William D. Foulkes, John R. Priest, Luis V. Syro, Henriett Butz, Michael D. Cusimano and Kalman Kovacs.* DICER1 gene mutations in endocrine tumors. Endocrine-Related Cancer, 2018. https://doi.org/10.1530/ERC-17-0509.

47. *Nikiforov Y.E., Nikiforova M.N.* Molecular genetics and diagnosis of thyroid cancer. Nat Rev Endocrinol, 2011.7(10):569-580.

48. *Nixon I.J., Whitcher M.M., Palmer F.L.* The impact of distant metastases at presentation on prognosis in patients with differentiated thyroid carcinoma. Thyroid, 2012. 22(9):884-889.

49. *Priya S., Patro P.K., Malyavantham K.* DICER1 mutations and dysregulated microRNA pathways in thyroid cancer. Endocr Pathol, 2014. 25(3):232-243.

50. *Pugh T.J., Yu W., Yang J., Field A.L., Ambrogio L., Carter S.L., Hill D.A.* Exome sequencing of pleuropulmonary blastoma reveals frequent biallelic loss of TP53 and two hits in DICER1 resulting in retention of 5p-derived miRNA hairpin loop sequences. Oncogene, 2014. 33(45), 5295-5302. https://doi.org/10.1038/onc.2014.150.

51. *Ragazzi M., Ciarrocchi A., Sancisi V.* The role of miRNA in thyroid carcinogenesis: A meta-analysis. Endocr Relat Cancer, 2015. 22(5).

52. *Rakheja D., Chen K.S., Liu Y., Shukla A. A., Schmid V., Chang T. C., Amatruda, J. F.* Somatic mutations in DROSHA and DICER1 impair microRNA biogenesis through distinct mechanisms in Wilms tumours. Nature Communications, 2014. 5, 4802. https://doi.org/10.1038/ncomms5802.

53. *Richards S., Aziz N., Bale S., Bick D., Das S., Gastier-Foster J., Rehm H.L.* Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine, 2015.17(5), 405–423. https://doi.org/10.1038/gim.2015.30.

54. *Sabbaghian N., Srivastava A., Hamel N., Plourde F., Gajtko-Metera M., Niedziela M., Foulkes W.D.* Germ-line deletion in DICER1 revealed by a novel MLPA assay using synthetic oligonucleotides. European Journal of Human Genetics, 2014. 22(4), 564–567. https://doi.org/10.1038/ejhg.2013.215.

55. *Scheithauer B.W., Horvath E., Abel T.W., Robital Y., Park S.H., Osamura R.Y., Kovacs K.* Pituitary blastoma: A unique embryonal tumor. Pituitary, 2012. 15(3), 365–373. https://doi.org/10.1007/s11102-011-0328-x.

56. *Schultz K.A., Stewart D.R., Bahubeshi A.* DICER1 syndrome: Clarifying the diagnosis, clinical features, and management of a pleiotropic tumor predisposition syndrome." J Clin Oncol, 2014. 32(7):728-734.

57. *Schultz K.A.P., Williams G.M., Kamihara J., et al.* DICER1 and associated conditions: Identification of at-risk

individuals and recommended surveillance strategies. Clinical Cancer Research, 2018. 24, 2251–2261. https://doi.org/10.1158/1078-0432.Ccr-17-3089.

58. *Seki M., Yoshida K., Shiraishi Y., Shimamura T., Sato Y., Nishimura R., Takita J. Biallelic* DICER1 mutations in sporadic pleuropulmonary blastoma. Cancer Research, 2014. 74(10), 2742–2749. https://doi.org/10.1158/0008-5472.can-13-2470.

59. *Siegel R.L., Miller K.D., Jemal A. Cancer statistics. CA Cancer J Clin*. 2020;70(1):7-30.

60. *Soares P., Lima J., Preto A.* Genetic alterations in poorly differentiated and undifferentiated thyroid carcinomas. Curr Genomics, 2011.12(8):609-617.

61. *Stewart D.R., Best A. F., Williams G.M., Harney L.A., Carr A.G., Harris A.K., Schultz K.A.P.* Neoplasm risk among individuals with a pathogenic germline variant in DICER1. Journal of Clinical Oncology, 2019. 37(8), 668–676. https://doi.org/10.1200/jco.2018.78.4678.

62. *Sugitani I., Fujimoto Y., Yamada K.* Prospectively enrolled, consecutive series of papillary thyroid carcinoma patients who underwent surgery for less than 2 cm tumors: Outcomes and prognostic factors in 1000 consecutive cases. J Clin Oncol, 2010. 28(17):2793-2798.

63. *Takeshita D., Zenno S., Lee W.C., Nagata K., Saig K., Tanokura M.* Homodimeric structure and double-stranded RNA cleavage activity of the C-terminal RNase III domain of human dicer. Journal of Molecular Biology, 2007. 374(1), 106–120. https://doi.org/10.1016/j.jmb.2007.08.069.

64. *Van Engelen K., Villani A., Wasserman J.D., Aronoff L., Greer M.L.C., Tijerin Bueno M., Druker H.* DICER1 syndrome: Approach to testing and management at a large pediatric tertiary care center. Pediatric Blood Cancer, 2018. 65(1), e26720. https://doi.org/10.1002/pbc.26720.

65. *Vedanayagam J., Chatila W.K., Aksoy B.A., Majumdar S., Skanderup A.J., Demir E., Lai E.C.* Cancer-associated mutations in DICER1 RNase IIIa and IIIb domains exert similar effects on miRNA biogenesis. Nature Communications, 2019. 10(1), 3682. https://doi.org/10.1038/s41467-019-11610-1.

66. *Verburg F.A., Reiners C., Hanscheid H.* Long-term survival in differentiated thyroid cancer: What has changed? Nat Rev Endocrinol, 2015.11(10):642-644.

67. *Vogelstein B., Papadopoulos N., Velculescu V. E., Zhou S., Diaz L.A., Kinzler K.W.* Cancer genome landscapes. Science, 2013. 339(6127), 1546–1558. https://doi.org/10.1126/science.1235122 .

68. *Volante M., Landolfi S., Chiusa L., Palestini N., Motta M., Codegone A., Torchio B., Papotti M.G.* Poorly differentiated carcinomas of the thyroid with trabecular, insular, and solid patterns: a clinicopathologic study of 183 patients. Cancer, 2004. 100:950–957. doi: 10.1002/cncr.20087.

69. *Wang Y., Chen J., Yang W., Mo F., Senz J., Yap D., Huntsman D. G.* The oncogenic roles of DICER1 RNase IIIb domain mutations in ovarian Sertoli-Leydig cell tumors. Neoplasia, 2015. 17(8), 650–660. https://doi.org/10.1016/j.neo.2015.08.003.

70. *Wu M.K., de Kock L., Conwell L.S., Stewart C.J. R., King B.R., Choong C.S., Foulkes W.D.* Functional characterization of multiple DICER1 mutations in an adolescent. Endocrine-related Cancer, 2016. 23(2), L1–L5. https://doi.org/10.1530/ERC-15-0460.

71. *Wu M., Sabbaghian N., Xu B., Addidou-Kalucki S., Bernard C., Zou D., Foulkes, W. Biallelic* DICER1 mutations occur in Wilms tumours. Journal of Pathology, 2013. 230(2), 154–164. https://doi.org/10.1002/path.4196.

72. *Xing M.* BRAF mutation in thyroid cancer. Endocr Relat Cancer, 2005. 12(2):245-262.

73. *Zehir A., Benayed R., Shah R.H., Syed A., Middha S., Kim H.R., Berger M.F.* Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nature Medicine, 2017. 23(6), 703–713. https://doi.org/10.1038/nm.4333.

Information about authors:

Mussazhanova Zh.B.– associated professor, phD Al-Farabi Kazakh National University, Almaty, Kazakhstan e-mail: mussazhanova.zh@gmail.com; Department of Tumor and Diagnostic Pathology, Atomic Bomb Disease Institute, https://orcid.org/0000-0002-7315-7725, Nagasaki, Japan

Dushimova Z.D. – k.m.s. in department of fundamental medicinemedical department and healthcare, https://orcid.org/0000-0003-0791-4246, Al-Farabi Kazakh National University, e-mail: dushimova.zaure@kaznu.edu.kz, Almaty, Kazakhstan

Kozykenova Zh.Y. – phD, head of department pathological physiology, https://orcid.org/0000-0001-7420-2279, NCJSC "Semey Medical University, e-mail: zhanna.kozykenova@smu.edu.kz, Semey, Republic of Kazakhstan

Pak L.A. - professor, phD head of Department of Clinical Oncology and Nuclear Medicine https://orcid.org/0000-0002-5249-3359, NCJSC "Semey Medical University," e-mail: laura.pak@smu.edu.kz, Semey, Republic of Kazakhstan

Toktabayeva B.Zh. – Candidate of Medical Sciences, Acting Associate Professor, Department of Propaedeutics of Children's Diseases NCJSC «Semey Medical University», 103 Abay street, Semey, 071400, Kazakhstan; Email:bakytkul.toktabayeva@smu.edu.kz; Phone number:+7(701)150-84-20. https://orcid.org/0000-0001-5899-1247

Zhazykbayeva L.K. – k.m.s internal diseases department, https://orcid.org/0000-0001-6529-284X, NCJSC "Semey Medical University," e-mail: lashyn.zhazykbayeva@smu.edu.kz, Semey, Republic of Kazakhstan

Rakhmankulova A.M. - a PhD student of the Department of Clinical Oncology and Nuclear Medicine, https://orcid.org/0000-0003-3307-413X, NCJSC "Semey Medical University," e-mail: rakhmankulova.aidana1992@gmail.com, Semey, the Republic of Kazakhstan;

Corresponding Author:

Yerketayeva A.Kh. – a Ph.D. student of the Department of Clinical Oncology and Nuclear Medicine, NCJSC "Semey Medical University," Semey, Republic of Kazakhstan

Address: 071400, Republic of Kazakhstan, Semey, Abay Street, 103.

E-mail: aki04121994@gmail.com

Phone: + 7 775 722 60 91.