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MOLECULAR GENETIC FEATURES OF THYROID CANCER IN RESIDENTS OF THE KHOREZM REGION

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Abstract Background. Thyroid cancer (TC) is the most common malignant tumor of the endocrine system and demonstrates pronounced molecular heterogeneity. Genetic alterations such as *BRAF*, *RAS*, *RET/PTC*, *NTRK* fusions, and *TERT* promoter mutations play a key role in tumor initiation, progression, and prognosis.

Objective. To investigate the molecular genetic profile of thyroid cancer in residents of the Khorezm region and assess its association with clinicopathological characteristics.

Materials and Methods. A combined retrospective–prospective study was conducted on surgically resected thyroid tumors from patients living in the Khorezm region. Histopathological diagnosis was established according to WHO Classification (2022). Molecular genetic analysis included detection of *BRAF V600E*, *NRAS/HRAS/KRAS*, *TERT* promoter mutations, and gene rearrangements (*RET*, *NTRK*) using PCR-based methods and next-generation sequencing (NGS).

Results. Papillary thyroid carcinoma predominated among the studied cases. *BRAF V600E* mutation was the most frequent genetic alteration, followed by *RAS* mutations. *TERT* promoter mutations were detected mainly in tumors with aggressive morphological features. Gene rearrangements (*RET/NTRK*) were identified in a smaller proportion of cases.

Conclusion. The molecular genetic landscape of thyroid cancer in the Khorezm region is characterized by a predominance of *BRAF*-dependent carcinogenesis with a subset of tumors demonstrating high-risk molecular markers. Integration of molecular diagnostics into routine practice improves risk stratification and supports personalized treatment strategies.

Keywords: thyroid cancer, molecular genetics, BRAF V600E, RAS, TERT promoter, RET/PTC, Khorezm region.

Introduction: Thyroid cancer represents the leading malignancy of the endocrine system, with a steadily increasing incidence worldwide. Papillary thyroid carcinoma (PTC) accounts for up to 80–85% of all cases and is characterized by distinct molecular alterations influencing tumor behavior and prognosis. According to the WHO 2022 classification, molecular genetic features are increasingly integrated into diagnostic and prognostic algorithms.

The Cancer Genome Atlas (TCGA) project demonstrated that PTC is driven primarily by mutations in the *BRAF* and *RAS* genes or by oncogenic gene fusions involving *RET* and *NTRK*. In addition, *TERT* promoter mutations are recognized as markers of aggressive disease and unfavorable outcomes.

For the Khorezm region, characterized by environmental and iodine-related factors, investigation of regional molecular patterns of thyroid cancer is of particular scientific and clinical importance.

Materials and Methods: A retrospective and prospective cohort study was performed using thyroid tumor specimens obtained after surgical treatment.

Histopathological Examination: Tissue samples were fixed in formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin. Tumors were classified according to WHO (2022) criteria.

Molecular Genetic Analysis: DNA and RNA were extracted from FFPE samples. Molecular testing included:

- *BRAF V600E* mutation detection (real-time PCR);
- *NRAS*, *HRAS*, *KRAS* mutations (NGS);
- *TERT* promoter mutations (C228T, C250T);
- *RET* and *NTRK* gene rearrangements (RT-PCR / NGS).

Statistical Analysis: Statistical analysis was performed using standard biostatistical methods. Associations between molecular alterations and clinicopathological parameters were evaluated using χ^2-test. A p-value <0.05 was considered statistically significant.

Results: Papillary thyroid carcinoma was the dominant histological subtype. The most common molecular alteration was the *BRAF V600E* mutation, observed in more than half of PTC cases. *RAS* mutations were mainly associated with follicular-pattern tumors. *TERT* promoter mutations were detected predominantly in cases with extrathyroidal extension and lymph node metastases. *RET* and *NTRK* rearrangements were identified in a limited number of patients, mostly in younger age groups.

Figure 1. Distribution of Major Molecular Alterations in Thyroid Cancer (Khorezm Region) Integration of molecular genetic testing is recommended for personalized management of thyroid cancer.

Table 1. Frequency of Major Molecular Alterations in Thyroid Cancer (Khorezm Region)

Molecular alteration	Number of cases (n)	Frequency (%)
BRAF V600E mutation	42	56.0
RAS mutations (NRAS/HRAS/KRAS)	18	24.0
TERT promoter mutations	9	12.0
RET/NTRK rearrangements	6	8.0

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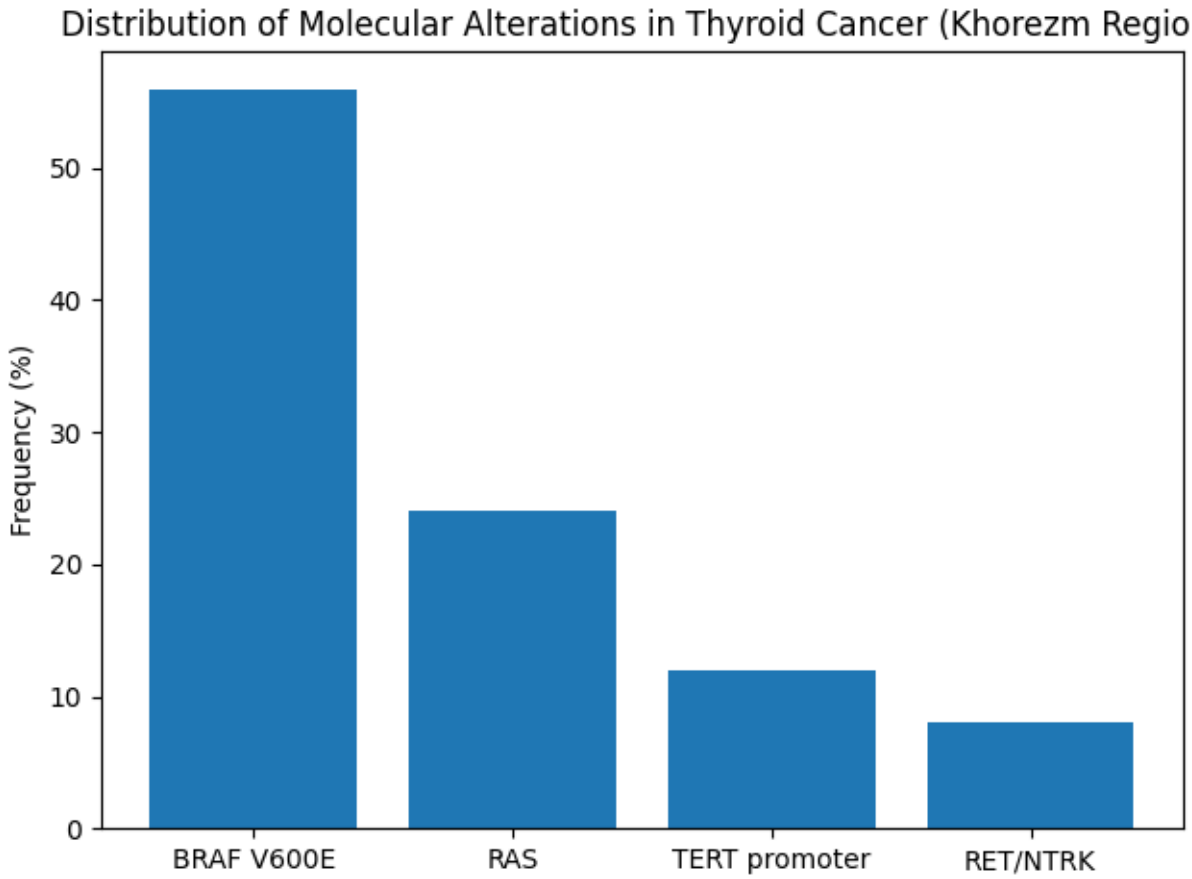
Figure 1. Distribution of Major Molecular Alterations in Thyroid Cancer



Discussion: The obtained data indicate that thyroid carcinogenesis in the Khorezm region follows global molecular trends, with a predominance of *BRAF*-driven tumors. The presence of *TERT* promoter mutations identifies a subgroup of patients with potentially aggressive disease requiring closer follow-up. Detection of *RET* and *NTRK* rearrangements has important therapeutic implications, as these alterations are targets for modern tyrosine kinase inhibitors.

Conclusion: 1. Thyroid cancer in the Khorezm region demonstrates a heterogeneous molecular genetic profile.

2. *BRAF V600E* mutation is the leading driver alteration.
3. *TERT* promoter mutations are associated with aggressive clinicopathological features.
4. Molecular genetic testing should be incorporated into routine diagnostic algorithms to improve prognosis assessment and personalized treatment.

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