

Molecular-Genetic Aspects in The Diagnosis of Odontogenic Tumors

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Abstract: In recent years, the overall number of diagnosed benign odontogenic tumors has increased substantially. Odontogenic tumors of epithelial origin are a group of diseases that attract considerable clinical interest. Diagnosis is challenging because of their marked heterogeneity, low incidence, and substantial morphological variation within individual tumor subgroups. Objective: to improve diagnosis and predict the clinical course of odontogenic tumors with consideration of their molecular-genetic characteristics. The studies showed that detection of the BRAF V600E mutation was associated with a 2.7-fold increase in the risk of developing odontogenic tumors. The proposed diagnostic algorithm for patients with benign odontogenic tumors is based on trephine biopsy followed by pathomorphological and genetic examination of the obtained material.

Keywords: Molecular-genetic testing; odontogenic tumors; BRAF V600E; mandibular ameloblastoma.

Introduction: “Keratocystic” lesions rank first in frequency among similar tumors of the jaw bones. The radiographic appearance of ameloblastomas may resemble almost any cystic lesion, potentially leading to misinterpretation and inadequate treatment.

The gold standard for diagnosing these conditions is the combination of clinical, radiological, and pathomorphological findings. In contemporary practice, however, this combination alone is insufficient, because it can be difficult to determine whether an odontogenic tumor is predisposed to locally aggressive growth [4,5].

Therefore, the scope of investigation needs to be expanded to improve the detection of oncological conditions in the maxillofacial region and the quality of surgical care for jaw lesions through an integrated approach incorporating molecular-genetic testing.

Until 2014, the molecular pathogenesis of ameloblastoma was largely unknown. However, a growing number of publications have reported the BRAF V600E mutation in patients with ameloblastoma (Kurppa K.J., Catón J., Morgan P.R., 2014; Maryam Soltani, 2017; E.G. Sviridov, 2019). In some studies, this mutation was detected in 82% of the ameloblastoma cases analyzed (Diniz M.G., Gomes C.C., Guimarães B.V., 2015). In addition to BRAF mutations, mutations in other genes of the MAPK pathway have been described. Mutations in the RAS gene family, including KRAS, NRAS, and HRAS, were found in 20% of ameloblastomas (Kurppa K.J., Catón J., Morgan P.R., Journal of Pathology, 2014).

Thus, scientific data on genetic alterations in patients with odontogenic tumors remain limited. Mutations have been reliably described only for certain

histological types, and the molecular-genetic changes in odontogenic tumors in the Uzbek population have not been investigated. Clinicians need information about these changes because conventional morphological and radiological methods are not always sufficient for an accurate, early diagnosis or for predicting the development and clinical course of this pathology.

Study objective

To improve the diagnosis of odontogenic tumors and predict their clinical course based on their molecular-genetic characteristics.

METHODS

The study was conducted from 2020 to 2023 in the Department of Maxillofacial Surgery at the Tashkent State Dental Institute clinic and at the Tashkent Regional Branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology. A total of 69 patients with various odontogenic tumors underwent comprehensive examination, including standard clinical and laboratory tests, morphological and histological examinations, and molecular-genetic testing.

Based on medical history, clinical, radiological, and histological findings, patients were divided into two groups: Group 1 comprised 52 patients with ameloblastoma, and Group 2 comprised 17 patients with other odontogenic tumors (adenomatoid odontogenic tumor, dentinoma, cementoma, and odontogenic myxoma).

The patients ranged in age from 21 to 67 years. The mean age was 38.6 ± 1.4 years among men and 40.7 ± 2.08 years among women.

Patients were referred from other medical institutions in the city to the Department of Maxillofacial Surgery at the Tashkent State Dental Institute clinic and the Tashkent Regional Branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology for consultation and treatment because of suspected mandibular neoplasms. On admission, patients had radiographs and, in some cases, computed tomography scans.

Clinical and laboratory, radiological, molecular-genetic, histomorphological, and statistical investigations were performed to address the study objectives.

Samples for histological examination were obtained by incisional biopsy and examined in the morphological department of the Tashkent Regional Branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology. Depending on the thickness of the cortical plate, tissue was collected using a scalpel or trephine bur.

Multislice computed tomography (MSCT) of the maxillofacial region was performed in spiral mode using a Somatom Emotion 64 scanner (Siemens, Germany). Contrast-enhanced MSCT was performed after non-contrast imaging, with administration of the non-ionic contrast agent Unihexol (2 mL/kg of Unihexol 350 mg iodine/mL; Unique Pharmaceutical Laboratories, India), followed by scanning.

Magnetic resonance imaging (MRI) was performed using a 1.5-T scanner (Ingenia 1.5 T; Philips Medical Systems, Best, the Netherlands).

To identify potential predictors of tumor development, the BRAF gene polymorphism was investigated, including the frequency of the BRAF V600E mutation in odontogenic tumors and the relationship between mutation status and clinicopathological and prognostic characteristics. The BRAF gene polymorphic variant was selected for analysis based on published literature.

Molecular-genetic analysis of biomaterials (DNA) was performed at the Department of Molecular Medicine and Cell Technologies of the Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan. DNA samples were isolated from peripheral blood lymphocytes using a modified protocol.

BRAF gene polymorphism genotyping was performed by standard polymerase chain reaction (PCR) on CG-1-96 Corbett Research (Australia) and 2720 Applied Biosystems (USA) programmable thermal cyclers, using MedLab test systems (Russia) in accordance with the manufacturer's instructions. Statistical assessment of deviations in the distribution of genotypes of the studied DNA polymorphisms from the canonical Hardy–Weinberg equilibrium (HWE) was carried out using computer software for genetic data analysis.

The study material included DNA obtained from tumor-tissue biopsies and tissue samples from metastatic lesions. Polymerase chain reaction is the basic method used to detect BRAF gene mutations. It is

straightforward to use and has good sensitivity, but it can detect only one mutation per run, whereas multiple mutations may be present and may all be diagnostically relevant. This can necessitate repeat tissue sampling, which is not always feasible. Sequencing can identify all BRAF gene mutations in a single tissue sample.

The BRAF gene is an important marker for evaluating tumor characteristics. It is primarily assessed during preoperative diagnosis and when selecting a drug for subsequent chemotherapy.

Statistical calculations were performed on a personal computer using Microsoft Excel 2010 under Windows 10. Data were analyzed using StatPlus v5/2009 and online calculators (Hardy–Weinberg equilibrium: <https://wpcalc.com/en/equilibrium-hardy-weinberg/>). A p-value of <0.05 was considered statistically

significant.

RESULTS

Analysis of sex distribution in the two study groups showed a statistically significant predominance of men among patients with ameloblastoma: 31 patients (59.6%) compared with women (reported as 22 patients, 40.4%; $p < 0.05$). In Group 2, women were slightly more numerous—9 (52.9%) compared with 8 men (47.1%); this difference was not statistically significant. The male-to-female ratio was 1.3:1 in the overall patient group, 1.4:1 in Group 1 (ameloblastoma), and 1:1.13 in Group 2 (other odontogenic tumors).

Age-based analysis showed that patients were 21–67 years old. The mean age in the overall group was 38.6 ± 1.4 years for men and 40.7 ± 2.08 years for women.

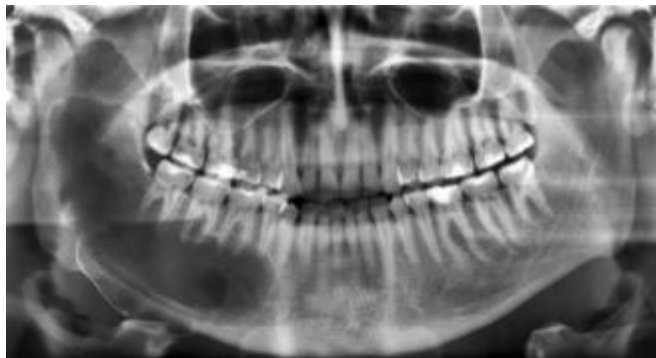


Fig. 2. Solid-type ameloblastoma of the right mandible.

Radiologically, solid and cystic forms of ameloblastoma can be distinguished. The solid form appeared as a

unilocular lesion (Fig. 2), whereas the cystic form showed a polycystic appearance (Fig. 3).



Fig. 3. Cystic ameloblastoma of the left mandible.

Radiographs showed heterogeneous radiolucency in the ameloblastoma in 80% of patients. In 20.4% of cases, the tumor affected the cortical plates of the jaw to varying depths, creating a false appearance of multiple cavities separated by bony septa. In 9.6% of cases, substantial penetration into the cortical plate caused complete destruction and extension into

adjacent soft tissues. The degree of bone expansion varied across affected sites. Because the tumors were located in the lateral portions of the mandibular body, the tumor cavity contained an impacted third molar in 20.4% of cases. In some cases, the lesion extended beyond the visible radiographic boundaries of bone involvement.

Radiographically, myxoma appears as a cyst-like, low-density lesion with indistinct borders, usually with a honeycomb pattern visible within it (Fig. 4).

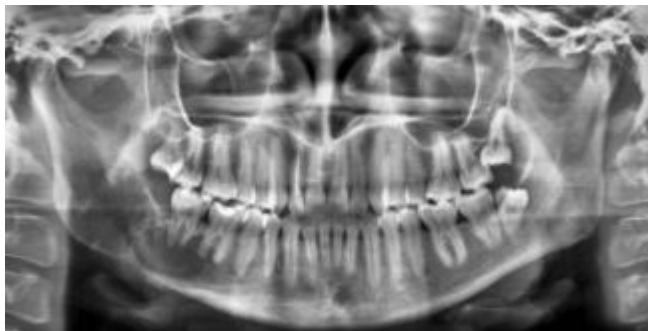


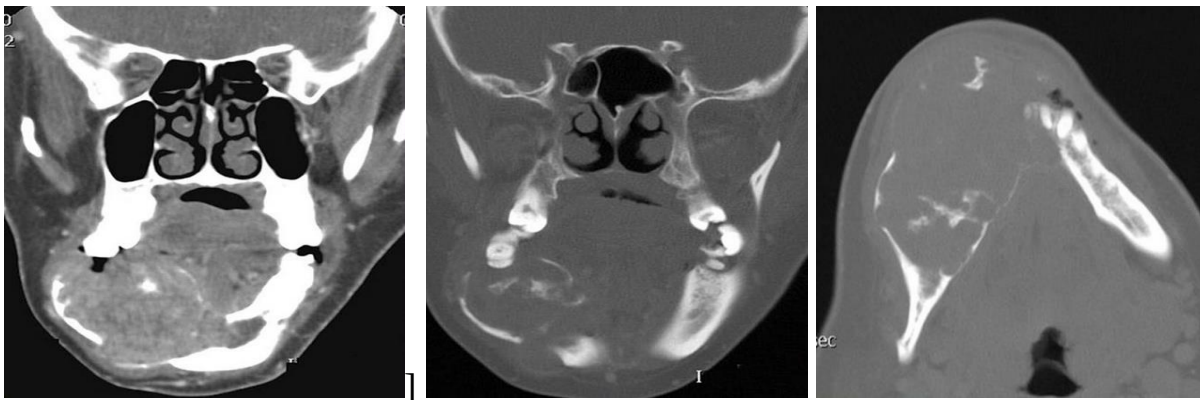
Figure 4. Myxoma of the right mandible.

For extensive tumor lesions, particularly those involving the maxilla and the upper facial bones, computed tomography is more appropriate than conventional radiographic techniques.

On MSCT, 21 patients with ameloblastoma (40.4%) had small tumors characterized by peripheral contrast enhancement only. The remaining 31 patients (59.6%) were described as having large masses extending beyond the bone, with a solid component showing moderate contrast uptake and low-density cystic areas. The source text also states that none of the 52 patients (100%) had extension beyond the bone; this statement appears inconsistent with the preceding description and is retained here as reported. On bone-window

MSCT, 21 patients (40.4%) had unilocular lesions, while the other 31 (59.6%) had multilocular masses with scalloped margins. A “soap-bubble” appearance was observed in 18 patients (34.6%), but this is not a pathognomonic sign of ameloblastoma.

Clinical Case 1. Patient D., aged 45 years. A: On a coronal MSCT section in the soft-tissue window, a large mass is visualized in the right mandibular body, with extension and destruction of the cortical bone. B, C: Coronal and axial MSCT sections of the anterior mandible show a heterogeneous solid-cystic mass extending into the right side, with septa and destruction of the cortical layer at this level.



Diagnostic significance and prognostic role of detecting BRAF gene mutations in patients with odontogenic tumors

Genetic testing demonstrated findings related to BRAF V600E expression, which was assessed in two groups. For analysis of BRAF gene polymorphism, participants were divided into Group 1, patients with histologically confirmed ameloblastoma (n = 52), and Group 2, patients with other odontogenic tumors (n = 17).

Among all patients with odontogenic tumors (n = 69), the frequency of the T allele was 84.1% and that of the A allele was 15.9%. Genotype frequencies were 68.1% for T/T and 31.9% for T/A; the A/A genotype was not observed in either study group (Table 1).

Table 1. Distribution and frequency of alleles and genotypes of the BRAF V600E polymorphism among all patients in the study group

Allele/genotype	n	%	χ^2	p	RR	95% CI	OR	95% CI
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						for RR		for OR
T	116	84.1	1.1	0.30	0.9	0.66–1.28	0.5	0.15–1.78
A	22	15.9	1.1	0.30	1.1	0.12–9.49	2.0	0.56–6.84
T/T	47	68.1	1.3	0.30	0.8	0.56–1.22	0.5	0.12–1.72
T/A	22	31.9	1.3	0.30	1.8	1.22–2.67	2.2	0.58–8.2

Comparison between the two groups showed that the T-allele frequency was 81.73% in Group 1 and 91.18% in Group 2; the A-allele frequencies were 18.27% and 8.82%, respectively. The T/T genotype frequencies were 63.5% and 82.4%, and the T/A genotype frequencies were 36.5% and 17.7%, respectively (Table

2).

Thus, the T allele and T/T genotype were the most common in both study groups. These findings require further investigation in a larger cohort from this population.

Table 2. Comparison of the distribution and frequency of alleles and genotypes of the BRAF V600E polymorphism in Groups 1 and 2

Allele/genotype	Group 1 n	Group 1 %	Group 2 n	Group 2 %	χ^2	p	RR	95% CI for RR	OR	95% CI for OR
T	85	81.73	31	91.18	1.7	0.20	0.9	0.61–1.32	0.4	0.12–1.52
A	19	18.27	3	8.82	1.7	0.20	1.1	0.13–9.52	2.3	0.66–8.11
T/T	33	63.5	14	82.4	2.1	0.20	0.8	0.47–1.26	0.4	0.1–1.41
T/A	19	36.5	3	17.7	2.1	0.20	2.1	1.27–3.38	2.7	0.71–10.21

It should be noted that other researchers have investigated the BRAF V600E mutation in remnants of normal odontogenic tissue and dental follicles associated with unerupted teeth to identify possible early oncogenic mutations that could lead to odontogenic tumorigenesis. However, the specific BRAF and KRAS mutations were not detected in any of the samples examined, supporting their absence in healthy tissue. In other words, polymorphism of this gene appears to be associated with pathological processes.

The findings of the present study are consistent with other studies examining a potential association between changes in genes involved in DNA damage repair and the development of ameloblastoma [1,2].

Sweeney et al. [3,4] identified BRAF mutations resulting in the substitution of valine with glutamic acid at codon 600 in 46% of ameloblastoma samples. SMO mutations were also identified and were predominant in maxillary ameloblastomas, whereas BRAF mutations were more frequent in mandibular lesions, as also observed in our study.

In the present study, analysis of allele distribution showed a higher frequency of the T allele than the A allele. The T-allele frequency was 91.2% in patients with other odontogenic tumors compared with 81.7% in patients with ameloblastoma; the corresponding A-allele frequencies were reported as 8.9% and 18.3%, respectively (Fig. 5).

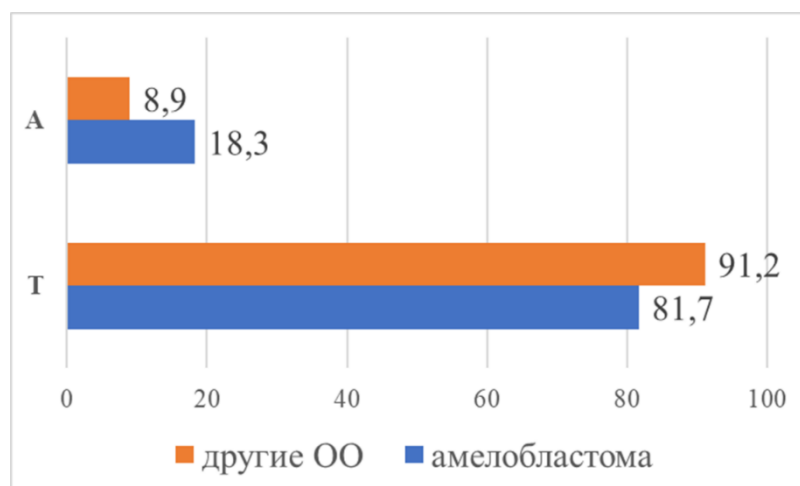


Figure 5. Frequency distribution of T and A alleles of the BRAF V600E polymorphism (T1799), rs113488022, in the study groups.

Analysis of the predictive performance of the polymorphism based on the T/T genotype in the two study groups showed relatively moderate sensitivity (0.63/0.68) and low specificity (Fig. 6), while a different pattern of activity was observed for the T/A genotype.

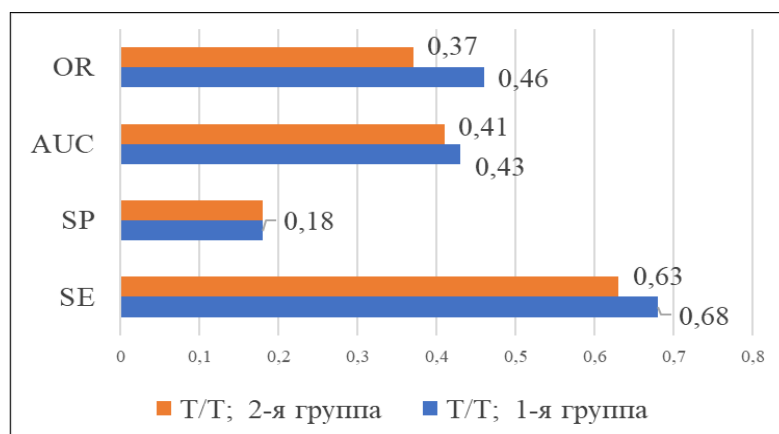


Figure 6. Predictive performance of the studied polymorphism based on the BRAF V600E T/T genotype.

CONCLUSIONS

1. Odontogenic tumors are characterized by slow, asymptomatic growth and are most often detected incidentally on radiographic examination. The main symptoms were facial asymmetry in 48 patients (92.3%) in Group 1 and pain during chewing in 15 patients (88.2%) in Group 2. Statistically significant differences between Groups 1 and 2 ($p \leq 0.05$) were observed for facial asymmetry, bulging of the oral vestibular fold, and pain at rest.
2. The study findings showed that detection of the BRAF V600E mutation was associated with a 2.7-fold increase in the risk of developing odontogenic tumors.
3. The proposed diagnostic algorithm for patients with benign odontogenic tumors is based on trephine biopsy followed by pathomorphological and genetic examination of the collected material.

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