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**The Prevalence and Prognostic Implications of
BRAF K601E Mutations in Thyroid Neoplasms:
A Systematic Review and Meta-analysis**

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 September 2024 and was last updated on 01 September 2024.

INTRODUCTION

Review question / Objective What is the histopathological association in thyroid masses with the K601E BRAF mutation, notably in comparison to the more common V600E mutation?

Rationale Given the biochemical differences between K601E and V600E mutants, including constitutive dimer versus monomer formations and variable inhibitor sensitivities, it is essential to clarify whether K601E-positive neoplasms constitute a clinically distinct entity or can be managed similarly to the more common V600E subtype.

Condition being studied Thyroid neoplasm, including papillary thyroid cancer, follicular thyroid cancer, poorly differentiated thyroid cancer, NIFTP, and follicular adenoma.

METHODS

Search strategy A systematic literature search was conducted using PubMed, Web of Science, and Embase databases to identify studies reporting the prevalence and prognostic value of BRAF K601E mutations in thyroid neoplasms. The search criteria included the following terms: (BRAF AND (K601E OR K601 OR K600) AND (Thyroid) AND (Cancer OR Carcinoma OR Adenoma OR Tumor OR Neoplasm)).

Participant or population Participants addressed in this review are individuals who have undergone excision of thyroid tissue, either surgically or through biopsy, with available pathology results and molecular testing of BRAF mutant subtype.

Intervention Not applicable.

Comparator Not applicable.

Study designs to be included Case series, single- and multi-institutional data reports and analyses.

Eligibility criteria The search was limited to human subjects with primary thyroid tumors that had data on K601E mutation status, histological classification, and/or prognostic indicators. V600E mutation data was also extracted for comparison. Only full-text articles written in English were considered. Case reports, meta-analyses, reviews, conference abstracts, and studies with incomplete mutational or clinical data were excluded.

Information sources Electronic databases.

Main outcome(s) The results have revealed that K601E-mutated tumors constitute a molecularly distinct subtype of thyroid masses and neoplasms when compared to the predominant BRAF V600E variant. Notably, we found stark differences in the histopathological distribution of K601E versus V600E mutations. K601E mutants were enriched in low-risk follicular-patterned lesions like NIFTP, FTC, and FA. In contrast, V600E predominantly occurred in conventional PTC and aggressive PDTC. These findings indicate that K601E identifies a subset of primarily indolent, follicular-derived neoplasms, whereas V600E is associated with high-risk differentiated and poorly differentiated carcinoma subtypes. We found a significantly lower rate of extrathyroidal extension in K601E compared to V600E mutants, indicative of less aggressive invasive potential. While extrathyroidal spread was attenuated in BRAF K601E mutants, metastatic capacity to regional lymph nodes was not equivalently reduced.

Data management Shared excel sheets.

Quality assessment / Risk of bias analysis Two investigators independently screened titles, abstracts, and full texts to determine study eligibility. Disagreements were resolved through discussion and consensus. For included studies, data was extracted on the year of publication, country, sample size, thyroid neoplasm histopathology, the prevalence of BRAF K601E and BRAF V600E mutations, extrathyroidal extension, lymph node status, recurrence, and mortality. The Newcastle-Ottawa scale was used to assess study quality and risk of bias.

Strategy of data synthesis RStudio was used for statistical analysis. Pooled prevalence and 95% confidence intervals were calculated for BRAF K601E and BRAF V600E mutation rates using the inverse variance method with arcsine transformation of proportions. For pooled

proportions, the Clopper-Pearson method was used to calculate confidence intervals for individual studies. Mean age was pooled using the inverse variance method on untransformed raw means. For pairwise comparisons, the DerSimonian-Laird estimator was used for tau². A continuity correction of 0.5 was applied in studies with zero cell frequencies. Risk ratios with 95% confidence intervals were computed to compare extrathyroidal extension and lymph node metastasis rates between K601E-mutated tumors, V600E mutants, and BRAF wild-type groups using the Mantel-Haenszel method. Heterogeneity was assessed using I² statistics, and the "Random model" was used in the presence of significant heterogeneity (I²>50%). Subgroup analyses were performed based on geographical region. Publication bias was evaluated with funnel plots and Egger's regression test.

Subgroup analysis The prevalence of BRAF K601E mutations varied across geographic regions. The mutation prevalence was highest in Italy and the United States. Rates were lower in cohorts from Korea and Portugal (Figure 5). In studies from the USA, the pooled BRAF K601E mutation rate was 3.31% (95% CI 1.40%-5.97%). For studies conducted in Italy, the K601E prevalence was significantly higher, accounting for 5.23% (95% CI 1.47%-11.11%). Korean studies reported a mutation rate of 1.78% (95% CI 0.41%-4.10%). Whereas studies from Portugal had the lowest K601E rate at 1.90% (95% CI 1.00%-3.09%).

Sensitivity analysis Sensitivity analysis was performed by omitting one study at a time to evaluate its influence on the pooled BRAF K601E mutation rate. Most studies did not substantially change the overall estimate. However, excluding two specific studies led to a deviation from the original 3% mutation rate, indicating that these two studies strongly influenced the meta-analysis results.

Language restriction English.

Country(ies) involved United States, Egypt, Saudi Arabia.

Keywords thyroid cancer; BRAF mutation; K601E; V600E; malignancy.

Dissemination plans Submission to "Head & Neck" journal for publication.

Contributions of each author

Author 1 - Eman Toraih - Author 1 assisted in data collection, analysis, and editing/review of the manuscript.

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Author 9 - Manal Fawzy - The author engaged in manuscript review and project oversight, as well as figure development and idea generation.

Author 10 - Emad Kandil - Offered overall oversight and management of the project, with initial idea generation and final manuscript review.

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