

Molecular Detection of ETV6-NTRK3 Gene Fusion in a Sample of Iraqi Breast Cancer Patients

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Abstract—Breast cancer (BC) remains a health challenge in Iraq, with patients presenting at younger ages and advanced stages. While gene fusions, particularly ETV6-NTRK3, are established oncogenic drivers in subtypes like secretory breast carcinoma (SBC), their prevalence within the Iraqi population remains unexplored. This study aimed to detect the *ETV6-NTRK3* gene fusion in Iraqi patients with BC to define its diagnostic specificity and clinicopathological correlates. Formalin-fixed paraffin-embedded tissue blocks from 60 women (aged 20–50 years) diagnosed with BC were collected. Samples were classified into three equal groups: SBC, Invasive Carcinoma of no special type, and invasive lobular carcinoma (n = 20 for each). The ETV6-NTRK3 fusion was detected using fluorescence *in situ* hybridization with a dual-color break-apart probe. The ETV6-NTRK3 fusion was detected exclusively in the SBC, with a prevalence of 100% (19/19 successfully scored cases), while it was absent in all scored cases of other groups, yielding a positive predictive value of 100% and a negative predictive value of 100%. Fusion-positive SBC tumors were associated with clinicopathological features: they were exclusively low to intermediate histological grade (Grades I-II) and predominantly presented at early pathological stages (Stage I-II: 84.2%). The fusion-positive cases were 93 times more likely to present with an early stage of disease compared with fusion-negative cases (odds ratio: 93.33; 95% confidence interval: 16.15–539.19). In conclusion, the ETV6-NTRK3 fusion may be a definitive molecular hallmark of SBC in Iraqi patients, and could demonstrate perfect diagnostic specificity and association with a less aggressive phenotype.

Index Terms—ETV6-NTRK3 fusion, Fluorescence *in situ* hybridization, Invasive carcinoma NST, Invasive lobular carcinoma, Secretory breast carcinoma.

I. INTRODUCTION

Breast cancer (BC) is a heterogeneous disease characterized by the uncontrolled growth of epithelial cells, typically originating in the milk ducts (ductal carcinoma) or lobules (lobular carcinoma) (Kerlikowske, et al., 2021). According

to the latest global cancer statistics reported by the Global Cancer Incidence, Mortality and Prevalence Database (GLOBOCAN) for 2022, BC remains the most common cancer diagnosed among women, with approximately 2.3 million cases and 670,000 associated deaths reported annually during that period (Bray, et al., 2024). Locally, BC occupies a critical position as the most common malignancy in Iraq, accounting for approximately 35.9% of all female cancers (Ali and Muslim, 2025). The biological complexity of BC is due to various genetic alterations, including point mutations, gene amplifications, and structural chromosomal rearrangements. The research in Iraq has focused either on germline mutations in genes such as *BRCA1* and *BRCA2* or somatic alterations like human epidermal growth factor receptor 2 (HER2) amplification (Al-Janaby, Al-Ani and Lafta, 2025; Hade and Hade, 2025). However, these genes do not represent the oncogenic drivers in all patients. Therefore, the development in molecular research has shifted toward gene fusions, which produce hybrid genes when two genes are fused together due to chromosomal translocations, inversions, or deletions (Cazzato, et al., 2025). Unlike simple mutations, gene fusions often create “chimeric” proteins with new functions, leading to the constitutive activation of signaling pathways that promote cell survival and uncontrolled proliferation (Gao, et al., 2018). The *ETV6-NTRK3* gene fusion is a primary event with significant clinical interest among the identified oncogenic drivers in BC. This fusion is the result of a balanced chromosomal translocation, t (12;15) (p13; q25), which fuses the 5’ end of the *ETV6* gene (ETS variant 6) on chromosome 12 with the 3’ end of the *NTRK3* gene (neurotrophic receptor tyrosine kinase 3) on chromosome 15 (Kinnunen, et al., 2023). This fusion creates a chimeric protein which acts as an always-on oncoprotein by stimulating the continuous activation of the kinase domain (Cocco, Scaltriti and Drilon, 2018). While this fusion gene is rare in general BC, it represents a diagnostic hallmark for the secretory breast carcinoma (SBC) subtype, appearing in most of confirmed cases (Boustros, et al., 2024). The identification of this fusion is clinically important, as it makes the tumors to be highly sensitive to newly approved TRK inhibitors, such as larotrectinib and entrectinib, thus provides an effective treatment for patients who may not respond to the traditional chemotherapy (Hong, et al., 2020; Alkashaf and Mohammed, 2024). Although the worldwide

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studies are focusing on NTRK fusions as “tumor-agnostic” biomarkers for targeted therapy, there is a lack of molecular data regarding their prevalence within the Iraqi population. Investigating ETV6-NTRK3 fusion in Iraqi patients is clinically vital, as BC in this region is usually diagnosed in younger women with advanced stages of tumor (Mohsin and Mohamad, 2024), and therefore identifying of this fusion could unlock access to tropomyosin receptor kinase (TRK) inhibitor therapies for patients who remain misclassified by traditional hormonal profiling. However, current diagnostic protocols in local hospitals rely on traditional immunohistochemistry for estrogen receptor, progesterone receptor, and HER2, while screening for gene fusions such as ETV6-NTRK3 is not performed (Al Alwan, 2022). This standard approach is insufficient for the identification of SBC, which is a rare subtype of BC and driven by a unique genetic mechanism rather than hormonal pathways (Stockley, et al., 2023). Without specific molecular screening for the *ETV6-NTRK3* gene fusion, these cases remain hidden within the general population of BC patients (Chawsheen, et al., 2025). This gap in molecular profiling may limit patients from accessing modern, life-saving treatments, such as TRK inhibitors, which have demonstrated high efficacy in fusion-positive cases (Westphalen, et al., 2021). Therefore, the aim of this study was to introduce a targeted molecular approach to detect the ETV6-NTRK3 fusion in a sample of Iraqi patients, demonstrating that the advanced genetic testing represents a highly reliable method for identifying this rare BC subtype.

II. MATERIALS AND METHODS

A. Participant Recruitment and Formalin-Fixed Paraffin-Embedded (FFPE) Tissue Collection

This study was conducted on archived FFPE BC tissue samples from 60 women aged 20–50 years, collected between October 2024 and October 2025 from the private pathology laboratories in Baghdad, Iraq. Data collection was fully completed before the preparation of this study. Samples were selected using a purposive stratified sampling method to ensure representation of the three histological subtypes included in this study and to facilitate comparative analysis between the rare subtype (SBC) and the more common subtypes (invasive lobular carcinoma [ILC] and invasive carcinoma of no special type [NST]). To minimize selection bias, all available preserved specimens meeting the inclusion criteria for these three categories were identified during the study period and selected sequentially until the target sample size for each group ($n = 20$) was reached. Clinicopathological data, including histological grade and pathological stage, were retrieved from the patients’ archived pathology records. Additionally, the histopathological classification was achieved by the pathologists who were blinded to molecular analysis. Ethical approval of this study was obtained from the Research Ethics Committee at the Institute of Genetic Engineering and Biotechnology for Postgraduate Studies, University of Baghdad, Iraq (Approval No. IGB-ETH/I-001)

dated October 02, 2024. Due to the use of archived tissue samples, a waiver of informed consent was granted by the Ethics Committee. Patients outside the specified age range and samples with insufficient tissue material for molecular analysis were excluded.

B. Hematoxylin and Eosin (H&E) Staining

Three μm -thick sections were cut from each FFPE block and stained with H&E according to standard protocols to confirm the histological diagnosis and ensure adequate specimen quality. All slides were reviewed by a consultant pathologist to determine the histological subtype and tumor grade (Hasan, et al., 2024).

C. Fluorescent *in situ* Hybridization (FISH) Technique

The detection of *ETV6-NTRK3* gene fusion was performed using fluorescence *in situ* hybridization (FISH) on 3- μm thick FFPE sections. A custom CytoCell myProbes ETV6/NTRK3 Dual Color fusion probe (Oxford Gene Technology, Cambridge, UK) was used. The probe set was designed to hybridize to the t(12;15) (p13;q25) translocation, with the ETV6 (12p13.2) region labeled in green and the NTRK3 (15q25.3) region labeled in red. Slides were pre-treated and co-denatured at 75°C for 10 min, followed by hybridization at 37°C for 24 h. Post-hybridization washes were performed, and nuclei were counterstained with 4',6-diamidino-2-phenylindole. Signal evaluation was conducted using a fluorescence microscope equipped with appropriate filters (Ammar and Altaee, 2022).

D. Signal Interpretation and Scoring

The signal interpretation was evaluated according to the recommendation of the European Cytogeneticists Association as follows (Marchiò, et al., 2019):

- Normal pattern (Negative): In a normal diploid cell, the expected signal pattern is 2 green and 2 red signals, representing the two intact copies of chromosome 12 (ETV6) and chromosome 15 (NTRK3), respectively.
- Fusion pattern (Positive): The presence of the t(12;15) (p13; q25) translocation results in one green, one red, and one yellow/gold fusion signals. The fusion signals appear when the green and red probes overlap or are situated less than one signal diameter apart.

E. Cut-off and Validation

A sample was considered positive for the *ETV6-NTRK3* gene fusion if the fusion signal pattern was observed in >15% of the counted nuclei based on international guidelines (Wu, et al., 2021).

F. Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 26.0 (IBM Corp., Armonk, NY, USA). Continuous data (age) were expressed as mean $\pm$ standard deviation. The one-way analysis of variance, Chi-square test, and Mann–Whitney U test were

used to compare age across the three histological groups, while the independent t-test compared age between fusion-positive and fusion-negative groups. Categorical variables (grade, stage, fusion status) were analyzed using Fisher's Exact Test. The diagnostic performance of the fusion was reported as positive and negative predictive values (PPV, NPV) with 95% confidence intervals (CI) using the Wilson Score method. The association between fusion status and disease stage was quantified using odds ratio (OR) with 95% CIs. A $p < 0.05$ was considered statistically significant (Mishra, et al., 2019; Sullivan, 2023).

III. RESULTS

A. Clinicopathological Characteristics

The clinicopathological characteristics of the 60 patients classified by histological subtypes are summarized in Table I. The study included 20 patients each in the SBC, NST, and ILC groups. The mean age of all patients was 38.6 ± 8.5 years, with no significant difference ($p = 0.992$). Fig. 1 shows a section stained with H&E for the three subtypes.

Significant differences were observed in grade and pathological stage of tumors. SBCs were low-grade, with 45.0% classified as Grade I and 50.0% as Grade II. In

contrast, NST and ILC tumors were frequently high-grade, with 45.0% of NSTs and 50.0% of ILCs categorized as Grade III ($p < 0.001$). Similarly, SBC cases were diagnosed at significantly earlier pathological stages, with 45.0% and 35.0% of patients presenting at Stage I and Stage II, respectively, and no cases identified at Stage IV. Conversely, the majority of NST (60.0%) and ILC (55.0%) tumors were diagnosed at Stage III, with a substantial proportion presenting at Stage IV (35.0% and 40.0%, respectively; $p < 0.001$). No significant association was found between tumor laterality and histological subtype ($p = 0.274$).

B. Association of Histological Type with Clinical Risk

The correlation between histological subtype and clinical risk profiles is presented in Table II. SBCs were significantly associated with risk profiles compared to NST and ILC. Regarding tumor grade, SBCs were low-grade (45.0% Grade I), whereas the majority of NST (90.0%) and ILC (80.0%) tumors were categorized as intermediate or high-grade (Grade II-III) ($p < 0.001$). In pathological stage distribution: 80.0% of SBCs were diagnosed at an early stage (I-II), compared to only 5.0% of both NST and ILC tumors. Consequently, 95.0% of NST and ILC cases were categorized as advanced stage (III-IV), versus 20.0% of SBCs ($p < 0.001$).

TABLE I
COMPARISON OF CLINICOPATHOLOGICAL CHARACTERISTICS (N=60)

Characteristic	Total (n=60)	SBC (n=20)	NST (n=20)	ILC (n=20)	p-value
Age (years)					
Mean $\pm$ SD	38.6 $\pm$ 8.5	38.4 $\pm$ 9.6	38.6 $\pm$ 8.2	38.8 $\pm$ 8.2	0.992*
Median (IQR)	39.5 (31.8–46.0)	41.0 (28.5–48.3)	39.0 (34.5–46.8)	38.0 (33.0–46.0)	
Histological Grade, n (%)					
Grade I	15 (25.0)	9 (45.0)	2 (10.0)	4 (20.0)	<0.001[†]
Grade II	25 (41.7)	10 (50.0)	9 (45.0)	6 (30.0)	
Grade III	20 (33.3)	1 (5.0)	9 (45.0)	10 (50.0)	
Pathological stage, n (%)					
Stage I	10 (16.7)	9 (45.0)	1 (5.0)	0 (0.0)	<0.001[†]
Stage II	8 (13.3)	7 (35.0)	0 (0.0)	1 (5.0)	
Stage III	27 (45.0)	4 (20.0)	12 (60.0)	11 (55.0)	
Stage IV	15 (25.0)	0 (0.0)	7 (35.0)	8 (40.0)	
Tumor laterality, n (%)					
Left	31 (51.7)	8 (40.0)	11 (55.0)	12 (60.0)	0.274 [†]
Right	29 (48.3)	12 (60.0)	9 (45.0)	8 (40.0)	

*p-value from one-way ANOVA. [†]p-value from Fisher's Exact Test. SBC: Secretory breast carcinoma, NST: Invasive carcinoma of no special type, ILC: Invasive lobular carcinoma, SD: Standard deviation; IQR: Interquartile range. Bold values indicate statistically significant differences ($p < 0.5$)

TABLE II
CORRELATION OF HISTOLOGICAL TYPE WITH CLINICAL RISK PROFILE (N=60)

Risk profile	SBC (n=20) (%)	NST (n=20) (%)	ILC (n=20) (%)	p-value*
Grade risk				
Low-grade (I)	9 (45.0)	2 (10.0)	4 (20.0)	<0.001
Intermediate/High-grade (II-III)	11 (55.0)	18 (90.0)	16 (80.0)	
Stage risk				
Early stage (I-II)	16 (80.0)	1 (5.0)	1 (5.0)	<0.001
Advanced stage (III-IV)	4 (20.0)	19 (95.0)	19 (95.0)	
Composite high-risk [†]				
Yes (Grade III and/or Stage IV)	1 (5.0)	14 (70.0)	16 (80.0)	<0.001
No	19 (95.0)	6 (30.0)	4 (20.0)	

*p-value from Fisher's Exact Test. [†]Composite High-Risk defined as the presence of either poorly differentiated histology (Grade III) or distant metastasis (Stage IV), indicators of aggressive disease. SBC: Secretory breast carcinoma, NST: Invasive carcinoma of no special type, ILC: Invasive lobular carcinoma. Bold values indicate statistically significant differences ($p < 0.5$)

Based on the high-risk definition (Grade III or Stage IV), very few SBC patients (5.0%) were high-risk. In contrast, the majority of NST (70.0%) and ILC (80.0%) patients were classified as high-risk ($p < 0.001$).

C. Detection of ETV6-NTRK3 Fusion

The diagnostic performance of the ETV6-NTRK3 fusion across histological subtypes is shown in Table III. The characteristic fusion signal pattern in a positive SBC is shown in (Fig. 2) and the normal signal pattern in a fusion-negative NST and ILC is shown in (Fig. 3).

The analysis was based on 56 of the 60 cases that were successfully scored. Four cases were excluded because of technical issues during slide preparation. The fusion was exclusively detected in SBC. All 19 scored SBC cases were fusion-positive (100%). In contrast, none of the 18 that scored NST or 19 that scored ILC harbored the fusion (0% each). Overall, the fusion was present in 19 of 56 scored cases (33.9%). Based on these results, the presence of the ETV6-NTRK3 fusion had a PPV of 100% for confirming an SBC diagnosis. Its absence had a NPV of 100% for ruling

out SBC among histologically diagnosed NST and ILC cases.

D. Association between Age and ETV6-NTRK3 Fusion

A comparison of age between fusion-positive and fusion-negative cases is presented in Table IV, based on the 56 scored samples. No significant association was observed between age and fusion status. The mean age was similar between fusion-positive (38.4 ± 9.6 years) and fusion-negative (38.7 ± 8.1 years) groups ($p = 0.897$). Similarly, there was no significant difference when comparing median ages (41.0 vs. 39.0 years, $p = 0.824$) or when categorizing patients by age 40 as a cutoff ($p = 0.919$).

E. Association between Histological Grade and ETV6-NTRK3 Fusion

The relationship between histological grade and ETV6-NTRK3 fusion status is shown in Table V. All 19 fusion-positive tumors (100.0%) were low or intermediate grade (Grade I or II) ($p < 0.001$). Notably, nearly half (9/19; 47.4%) were Grade I. In stark contrast, none of the fusion-positive

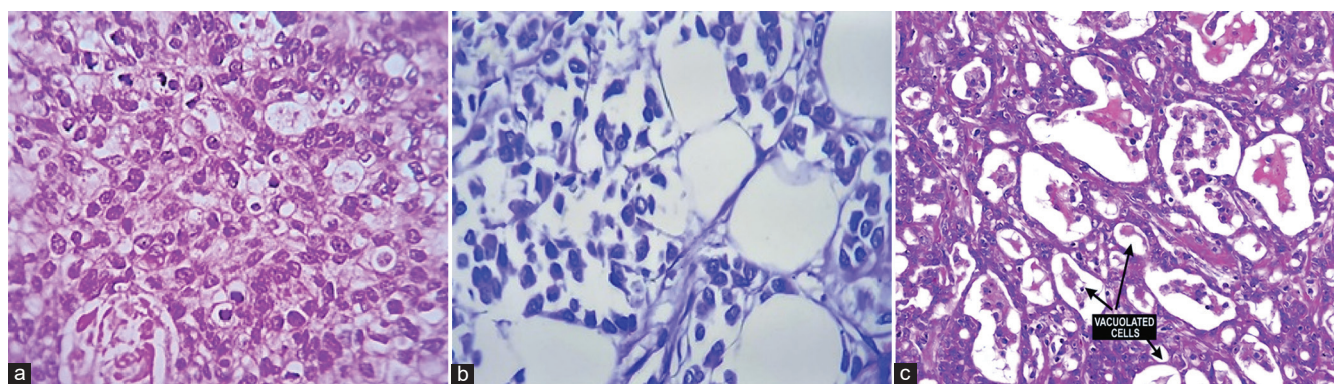


Fig. 1. Representative hematoxylin and eosin staining of the three breast carcinoma subtypes. (a) Invasive carcinoma of no special type. (b) Invasive lobular carcinoma (note single-file pattern). (c) Secretory breast carcinoma showing secretory material and vacuolated cells (highlighted by the arrows).

TABLE III
FREQUENCY AND DIAGNOSTIC SPECIFICITY OF ETV6-NTRK3 FUSION ANALYSIS BASED ON 56 SUCCESSFULLY SCORED CASES (EXCLUDES 4 “NOT SCORED”)

Histological type	Scored cases (n)	Fusion-positive, n (%)	95% CI for prevalence	PPV* (%)	NPV† (%)
SBC	19	19 (100.0)	82.4–100.0	100	-
NST	18	0 (0.0)	0.0–18.5	-	100
ILC	19	0 (0.0)	0.0–17.6	-	100
Overall	56	19 (33.9)	21.8–47.8	100	100

CI: Confidence interval (Wilson Score method). *PPV (Positive Predictive Value): Probability that a histologically diagnosed SBC harbors the fusion. †NPV (Negative Predictive Value): Probability that a histologically diagnosed NST or ILC does not harbor the fusion. SBC: Secretory breast carcinoma, NST: Invasive carcinoma of no special type, ILC: Invasive lobular carcinoma

TABLE IV
COMPARISON OF FUSION STATUS WITH AGE BASED ON 56 SCORED CASES

Age parameter	Fusion-positive (n=19)	Fusion-negative (n=37)	Test statistic	p-value
Mean±SD (years)	38.4±9.6	38.7±8.1	$t=-0.13^*$	0.897
Median (IQR) (years)	41.0 (28.5–48.3)	39.0 (34.0–46.0)	$U=336.5^†$	0.824
Age category, n (%)			$\chi^2=0.01^\ddagger$	0.919
≤40 years	10 (52.6)	20 (54.1)		
>40 years	9 (47.4)	17 (45.9)		

*Independent samples t-test. †Mann–Whitney U test. ‡Chi-square test. SD: Standard deviation, IQR: Interquartile range

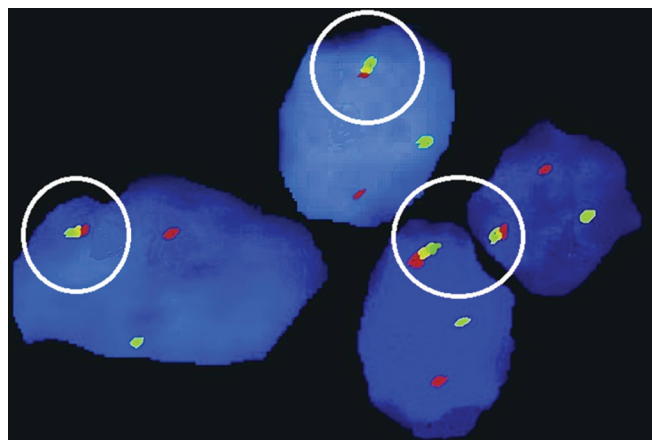


Fig. 2. Fluorescence *in situ* hybridization showing *ETV6-NTRK3* fusion-positive (secretory breast carcinoma). Green signal: ETV6; Red signal: NTRK3; Yellow/gold signal: Gene fusion.

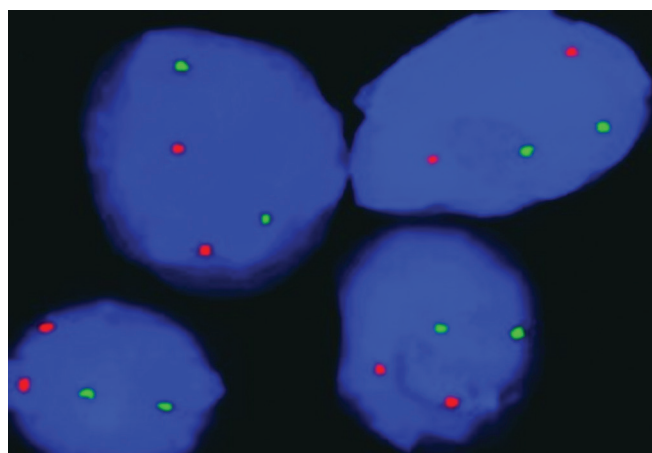


Fig. 3. Fluorescence *in situ* hybridization showing fusion-negative (invasive carcinoma of no special type and invasive lobular carcinoma). Normal pattern with two green (ETV6) and two red (NTRK3) signals, indicating no rearrangement.

cases were Grade III. Conversely, among the 37 fusion-negative tumors, 16 (43.2%) were high-grade (Grade III). The remaining fusion-negative cases were distributed across Grade I (16.2%) and Grade II (40.5%).

F. Association between Pathological Stage and ETV6-NTRK3 Fusion

The relationship between pathological stage and fusion status is detailed in Table VI. The vast majority (16/19; 84.2%) were diagnosed at an early stage (I or II), with 47.4% being Stage I while only 3 fusion-positive cases (15.8%) were Stage III ($p < 0.001$) and none were Stage IV. In contrast, fusion-negative tumors were predominantly advanced stage (III or IV), accounting for 94.6% of cases (35/37). Over half (64.9%) were Stage III, and 29.7% were Stage IV. Consequently, the odds of having an early-stage tumor were over 93 times higher for fusion-positive cases compared to fusion-negative cases (OR: 93.33, 95% CI: 16.15–539.19, $p < 0.001$).

TABLE V
COMPARISON OF FUSION STATUS WITH HISTOLOGICAL GRADE
BASED ON 56 SCORED CASES

Histological grade	Fusion-positive (n=19) (%)	Fusion-negative (n=37) (%)	p-value*
Grade I	9 (47.4)	6 (16.2)	<0.001
Grade II	10 (52.6)	15 (40.5)	
Grade III	0 (0.0)	16 (43.2)	
Grade grouping			<0.001
Low/Intermediate (I-II)	19 (100.0)	21 (56.8)	
High (III)	0 (0.0)	16 (43.2)	

*p-value from Fisher's exact test. Bold values indicate statistically significant differences ($p < 0.5$)

TABLE VI
COMPARISON OF FUSION STATUS WITH PATHOLOGICAL STAGE
BASED ON 56 SCORED CASES

Pathological stage	Fusion-positive (n=19) (%)	Fusion-negative (n=37) (%)	p-value*
Stage I	9 (47.4)	1 (2.7)	<0.001
Stage II	7 (36.8)	1 (2.7)	
Stage III	3 (15.8)	24 (64.9)	
Stage IV	0 (0.0)	11 (29.7)	
Stage grouping			<0.001
Early (I-II)	16 (84.2)	2 (5.4)	
Advanced (III-IV)	3 (15.8)	35 (94.6)	
OR for early stage	93.33	1.0 (Reference)	<0.001
95% CI for OR	16.15–539.19	-	

*p-value from Fisher's Exact Test. CI: Confidence interval, OR: Odds ratio. Bold values indicate statistically significant differences ($p < 0.5$)

IV. DISCUSSION

The present study represents the first molecular investigation of the *ETV6-NTRK3* gene fusion in a cohort of Iraqi BC patients, with particular focus on its association with the rare SBC subtype. The findings provide compelling evidence that the chromosomal rearrangement serves as a defining molecular hallmark of SBC within our population, defining a clinicopathological entity distinguished by prognostic characteristics. The concordance between histopathological and molecular findings confirmed the accuracy of conventional histology in diagnosing SBC and the specificity of the *ETV6-NTRK3* fusion for this tumor subtype.

The important finding of this study is that the *ETV6-NTRK3* gene fusion was found only in all scored cases of SBC (19/19), while the fusion was not observed in the other 37 scored cases of NST and ILC, as shown in Table III.

This finding matched other studies that identify *ETV6-NTRK3* as the key genetic marker for SBC, with higher detection rates (Kinnunen, et al., 2023). A meta-analysis in 2023 included 487 SBC cases detected *ETV6-NTRK3* fusion in 92.4%, with regional variations between Asian and Western populations (O'Haire, et al., 2023). The positive and negative predictive values for this study's population were 100% for each, which suggested that histopathological diagnosis of SBC is an indicator for the presence of this gene fusion. This finding was clinically significant, as the 2023 European Society for Medical Oncology guidelines recommend molecular testing for all suspected SBC cases

to identify patients who may benefit from targeted TRK inhibitor therapy (Rakaee, et al., 2023).

The results contrasted with other studies where ETV6-NTRK3 fusions have been identified in other BC subtypes. For instance, a study by (Zito Marino, et al., 2023) detected NTRK fusions in 0.5% of unselected triple-negative BCs, though none were the classic ETV6-NTRK3 variant. The complete absence of the fusion in NST and ILC cases may reflect either true biological differences in the genetic basis of BC in Iraqi patients or the limited sample size of non-SBC subtypes in this study. These results strongly support the WHO's decision to classify this type of breast tumor (SBC) as a separate category, due to it has its own unique genetic change (Md Nasir, et al., 2023).

The clinicopathological characteristics of fusion-positive SBC cases in this cohort show a consistent pattern of good prognostic features (Tables I, II, V and VI). Since the fusion-positive cases were low- to intermediate-grade tumors, this finding suggests that the ETV6-NTRK3 fusion may be associated with a less aggressive histopathological phenotype. This association between ETV6-NTRK3 fusion and lower histological grade has been linked to the fusion's specific cancer-causing pathway. Unlike high-grade carcinomas, which typically accumulate multiple genetic aberrations, the ETV6-NTRK3 fusion functions as a single-driver oncogene by constitutively activating the PI3K-AKT and MAPK signaling pathways, thereby promoting cellular transformation without requiring additional oncogenic alterations (Sesé, et al., 2025). Single-cell sequencing studies have shown that ETV6-NTRK3-driven tumors maintain more differentiated transcriptional programs compared to high-grade BCs (Medford, et al., 2023).

Even more important clinically is the clear difference in stage distribution, in which 84.2% of fusion-positive SBC cases presented at early pathological stages (I-II), compared to only 5.4% of fusion-negative cases ($p < 0.001$) (Table IV). Although the odds of having the disease in its early stages were 93 times higher in fusion-positive tumors (early stage OR: 93.33), the wide confidence interval (95% CI: 16.15–539.19) indicates limited precision of the estimate due to the small sample size; therefore, emphasis should be placed on the clinical observation (strong association of fusion-positive with an early stage of the disease) rather than the numerical value of the OR. This stage distribution is consistent with the biological characterization of SBC, which exhibits slow growth, low-grade, and limited ability to metastasize (Min, et al., 2022). A study by (Zhao, et al., 2024) included 52 SBC cases from Asia and reported 78% presenting as Stage I-II disease. Notably, although SBC often presents at an early stage, recent data have been shown that advanced or metastatic SBC still responds to TRK inhibitor therapy, with long-lasting benefits even in heavily treated patients (Demetri, et al., 2022). The early stage of disease in SBC of this cohort (80% of all SBC cases) may reflect either earlier detection due to increased awareness or a less aggressive biological behavior (Table II). This stage distribution had important treatment implications. Patients with fusion-positive, early-stage SBC may be decent candidates for breast-conserving

surgery and less additional therapy, especially when molecular testing is used to guide treatment decisions.

On addition, age at diagnosis did not differ significantly among the three histological subtypes or between the fusion-positive and fusion-negative groups (Tables I and IV). The mean age across all groups was approximately 38.6 years, which is younger than the typical BC population in Western countries, where the median age at diagnosis often exceeds 60 years (Elhawary, et al., 2025). This aligns with epidemiological data from Middle Eastern populations, where BC consistently presents a decade earlier than in Western cohorts (Rafiei, et al., 2023). A population-based study from Saudi Arabia reported a median age of 50 years for BC diagnosis (Abulkhair, et al., 2024). The consistent age distribution across subtypes in this study suggests that, while the BC burden shifts to younger women in Iraq, the age-specific risk for developing particular subtypes, including the rare SBC, follows a similar pattern.

The molecular results of this study were similar to, and on the other hand different from, those reported in other related studies. The similarity was observed with a retrospective study from Turkey by Yilmaz, et al., who investigated gene fusion in 17 cases and detected it in 94% (16/17) which is agreement with the present study (Yilmaz, et al., 2024), while the difference was noted with a study of Bell et al. who found the fusion only in 24% (11/45) which stands in strong contrast to the findings of this study (Rudzinski, et al., 2018). The histopathological features of SBC cases in this cohort (early stage and low grade) matches what has been seen in other studies. For example, a study by Ghilli et al. also found that 92% of their SBC cases were diagnosed at an early stage (Stage I-II), and all were low to intermediate grade (Ghilli, et al., 2018).

The current study has several limitations that should be considered. First, the small sample size, while sufficient to reflect the rarity of the SBC subtype, limits the generalizability of the findings. Second, the implementation of molecular techniques for the detection of ETV6-NTRK3 may be constrained by financial restrictions, emphasizing the need for selective use in clinically appropriate cases.

V. CONCLUSION

This study demonstrates that the *ETV6-NTRK3* gene fusion may serve as a diagnostic marker due to its strong association with SBC in this Iraqi cohort, and was associated with favorable clinicopathological features, as all fusion-positive tumors were low to intermediate grade and presented at an early pathological stage. These findings may help address the gap in Iraq's diagnostic system, which relies only on some immunological markers while ignoring the molecular diagnosis of gene fusion. To advance precision oncology in Iraq, the inclusion of ETV6-NTRK3 testing could be considered for the diagnosis of suspected SBC. Overall, these findings contribute to the global understanding of fusion-driven BCs and underscore the importance of integrating region-specific molecular diagnostics to support accurate diagnosis and optimize patient management.

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