BMC Cancer

RESEARCH Open Access

LYN mutations in breast cancer: hypothesis-generating evidence for an association with central nervous system metastasis and domain-level insights

Elif Kardelen Çağdaş[1,2*] and Berkay Çağdaş[3]

Abstract

Objectives Central nervous system (CNS) metastasis is a major driver of morbidity in metastatic breast cancer, yet the molecular determinants of CNS tropism remain incompletely defined. *LYN*, a Src-family kinase integrating receptor tyrosine kinase and integrin signaling, is a biologically plausible mediator of metastatic traits.

Design We performed a retrospective, multi-study analysis of publicly available breast cancer cohorts aggregated in cBioPortal. After harmonization and de-duplication, *LYN* status was determinable in 5,947 invasive carcinoma of no special type (NST) tumors across 29 studies. The primary endpoint was CNS metastasis at any time (Yes/No), harmonized via a prespecified controlled vocabulary (case-insensitive substring mapping). Somatic *LYN* variants (coding SNVs/indels) were collapsed to patient-level classes (missense-only; truncating if any nonsense/frameshift/splice). Variants with resolvable positions were mapped to Src-family modules (SH4/Unique, SH3, SH2, SH2-kinase linker, kinase). Two-group comparisons used two-sided Fisher's exact tests with exact 95% CIs; domain screens used omnibus χ^2 and Benjamini–Hochberg FDR control. A prespecified Firth logistic model evaluated truncating vs. missense within *LYN*-mutant tumors.

Setting Public cancer genomics repositories (cBioPortal); multi-institutional cohorts.

Participants 5,947 tumors across multi-study cohorts with *LYN* status available.

Interventions None.

Main outcome measures Primary: ever-CNS metastasis (yes/no). Secondary: distribution of *LYN* variant classes and domains (SH4/Unique, SH3, SH2, linker, kinase).

Results CNS metastasis occurred in 5/46 (10.9%) *LYN*-mutated tumors vs. 110/5,901 (1.9%) *LYN* wild-type tumors (odds ratio (OR) = 6.42; 95% confidence interval (CI), 2.49–16.56; $p = 0.0018$). The endpoint was captured as ever vs. never CNS involvement (event dates unavailable), precluding time-to-event inference. Within LYN-mutant cases, an exploratory domain analysis indicated that distributions differed by CNS status (omnibus χ^2 $p \approx 0.014$); a one-versus-rest signal at the SH4/Unique N-terminus was nominally significant and borderline after false discovery rate

*Correspondence:
Elif Kardelen Çağdaş
elifkardelencagdas@gmail.com

Full list of author information is available at the end of the article

(FDR) (unadjusted $p \approx 0.010$; $q \approx 0.052$; small in-domain $n = 3$). By mutation class, truncating vs. missense showed a higher CNS-positive proportion (28.6% vs. 7.9%) but did not reach significance (Fisher $p = 0.166$; alternatively framed OR = 4.22; exact 95% CI, 0.58–30.75; $p = 0.182$). Firth estimates were directionally consistent with wide profile CIs under sparse counts.

Conclusions Across pooled cohorts, *LYN* mutation is associated with increased odds of CNS metastasis, and domain context appears informative, with a small-sample, FDR-borderline enrichment at the SH4/Unique N-terminus. The truncating-class signal is exploratory given limited power. Signals by domain (notably SH4/Unique) are exploratory and require independent validation in larger, uniformly annotated datasets. Given small mutant denominators and ever-CNS endpoint capture, findings are hypothesis-generating and not actionable for risk stratification or treatment selection. Results motivate domain-aware annotation in future validation studies and mechanistic work.

Key messages

- What is already known: CNS metastasis is a major clinical problem in breast cancer; molecular determinants of brain tropism remain incompletely defined.
- What this study adds: Across pooled cohorts, any LYN mutation is associated with higher odds of CNS metastasis; domain context (notably SH4/Unique) may matter, albeit with small counts and FDR-borderline evidence.
- How this might affect research/practice/policy: Encourages domain-aware LYN annotation and targeted mechanistic work on membrane targeting/BBB traversal; not ready for risk stratification or treatment selection.

Keywords Breast cancer, CBioPortal, CNS metastasis, Domain mapping, Fisher's exact, Firth logistic, LYN, SH4/Unique, Src-family kinase

Introduction

Breast cancer remains a major cause of cancer morbidity and mortality, with a substantial share driven by CNS involvement [1]. As systemic therapies extend survival, brain and leptomeningeal metastases have greater clinical impact, yet the molecular drivers of CNS tropism are still poorly defined [2]. Brain colonization demands tumor-intrinsic programs—motility, invasion, survival—plus BBB transmigration and adaptation to the neural microenvironment [3]. Signaling modules that couple cell adhesion to RTK inputs and cytoskeletal regulation are thus strong candidates [4]. Src family kinases—including *LYN*—sit at this nexus, integrating integrin/FAK (focal adhesion kinase) signaling, ERBB (ERBB receptor family)/EGFR (epidermal growth factor receptor) cross-talk, and pathways controlling epithelial–mesenchymal transition (EMT), cell–cell junctions, and actin remodeling [5]. Although *LYN* copy-number/expression changes recur across cancers, the clinical relevance of specific *LYN* variants in breast cancer, particularly for CNS involvement, remains undefined [6], motivating a focused analysis of *LYN*'s structure–function context and an exploratory test of whether mutation class and domain location associate with CNS tropism.

LYN within the Src family: overview and relevance to breast cancer

LYN is a non-receptor tyrosine kinase (non-RTK) in the Src family (SFKs), conserved signal integrators that relay inputs from cell-surface receptors to control proliferation, survival, adhesion, motility, and cytoskeletal dynamics [7]. SFKs are rapidly engaged downstream of RTKs, integrins, GPCRs, immune and cytokine receptors, and phosphorylate substrates that scaffold focal adhesions, remodel actin, and amplify mitogenic/pro-survival cascades [5]. Because of this nodal position, small shifts in SFK activity or localization can produce outsized cellular effects. In immunity, *LYN* frequently acts as a negative regulator yet can also activate signaling, being required for both initiation and termination of B-cell responses (Fig. 1).

Physiologically, *LYN* tunes B-cell receptor signaling, Fc pathways in myeloid/mast cells, and tonic thresholds for activation/tolerance, acting positively or negatively depending on the complex and adaptors [8]. Upstream inputs include BCR (CD79A/B), CD5, CD19, CD22, Fc receptors, TLR2/4, and receptors such as EPOR, KIT, MPL, CXCR4, and IL-3/IL-5/CSF2 [9]. Outside hematopoiesis, LYN in epithelial tissues—including breast cancer—regulates cell–matrix adhesion, migration, EMT, and, via integrin/FAK and RTK (ERBB/EGFR) coupling to PI3K–AKT and RAS–RAF–MEK–ERK, enhances survival and proliferation [9, 10]. It also dampens signaling by phosphorylating ITIMs to recruit SHP-1/2 and SHIP-1.

LYN's qualitative output depends on conformation, localization, and scaffold/phosphatase balance, explaining context-dependent effects [11]. In breast cancer, altered *LYN* expression/mutation and rewired RTK–integrin–EMT networks plausibly promote CNS

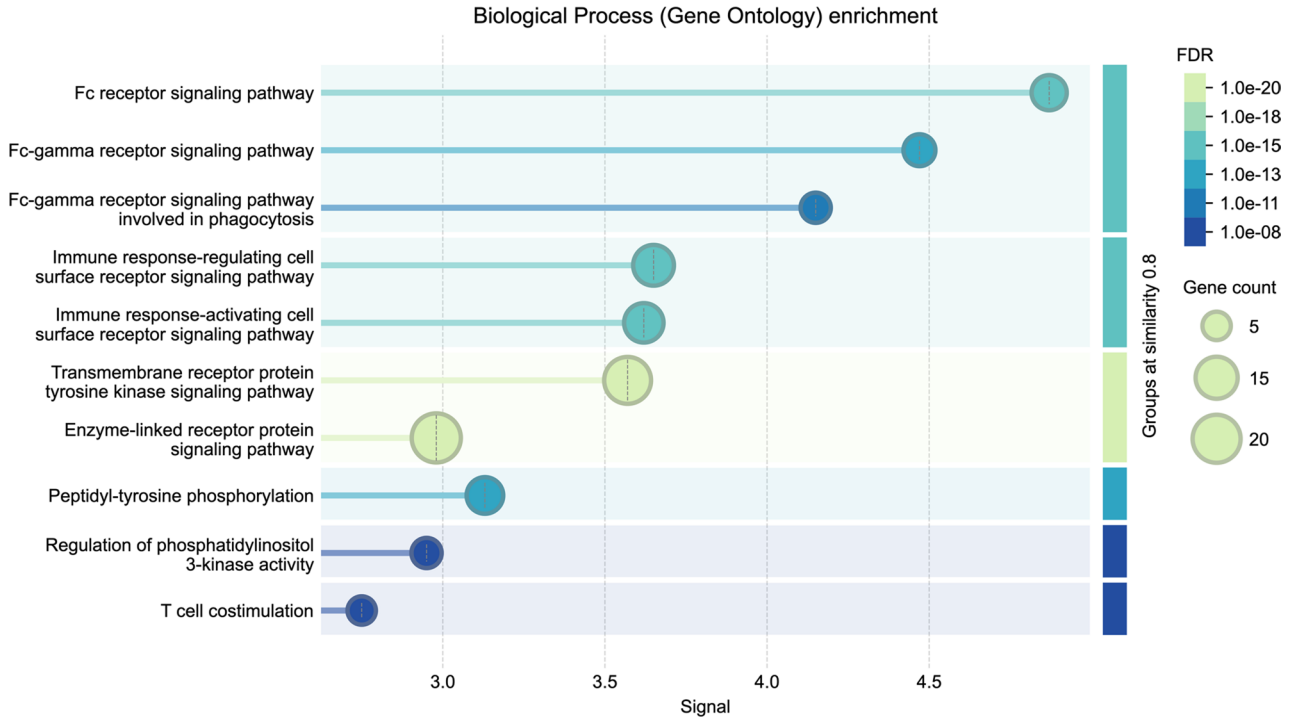

Fig. 1 Gene Ontology biological process (GO-BP) enrichment of the LYN-centered STRING network [8] Top enriched terms converge on immune-receptor signaling (B-cell/Fc/TLR), integrin–cytoskeleton interactions, leukocyte migration, and PI3K–AKT/MAPK cascades, consistent with adhesion, motility, and barrier-related pathways linked to CNS involvement

tropism—from intravasation and circulatory survival to endothelial adhesion and BBB transmigration [6, 12].

Molecular architecture of *LYN*

Like other Src family kinases (SFKs), *LYN* comprises modular domains that govern membrane targeting, autoinhibition, and stimulus-coupled activation:

- N-terminus/SH4/Unique: This region dictates subcellular localization, and alternative splicing fine-tunes these effects [5].
- SH3 domain: Binds proline-rich motifs in partners and in *LYN*'s own linker, clamping the kinase in a closed, autoinhibited state. High-affinity exogenous ligands can outcompete the intramolecular interaction to promote opening and priming [13].
- SH2 domain: Recognizes phosphotyrosine motifs. In autoinhibition, it engages the phosphorylated C-terminal regulatory tyrosine, reinforcing the closed conformation; binding to external pTyr ligands displaces this contact, activates the kinase, and recruits *LYN* to new complexes [13].
- SH2-kinase linker: A flexible, proline-rich segment that transmits conformational signals from the SH3/SH2 "regulatory head" to the catalytic core, acting as a mechanical gate that shifts the closed-open equilibrium and modulates catalytic efficiency [13].
- Kinase domain: The bilobal catalytic core contains the activation loop, whose phosphorylation state and conformation control substrate access and turnover. Subtle changes in loop dynamics can markedly alter activity and specificity [14].
- C-terminal regulatory tyrosine/CSK axis: CSK-mediated phosphorylation of the tail tyrosine promotes SH2 docking and autoinhibition; dephosphorylation by receptor-proximal phosphatases releases the clamp. The CSK-phosphatase balance thus sets a tunable rheostat on *LYN* activity [15].

Collectively, these modules create a conformational switch that integrates lipid targeting, intramolecular clamps, and catalytic licensing to couple localization to signaling (Fig. 2). In epithelial and breast cancer settings, perturbations in membrane targeting, regulatory interfaces, or the kinase core can yield distinct phenotypes in adhesion dynamics, EMT programs, and RTK/integrin responses, motivating tests of whether variant classes (e.g., truncations vs. interface/targeting missense changes) associate with CNS metastasis [6, 13–15].

LYN alterations in breast cancer

Copy-number and expression changes: Across cancers, amplification/overexpression of *LYN* has been reported more frequently than recurrent hotspot mutations,

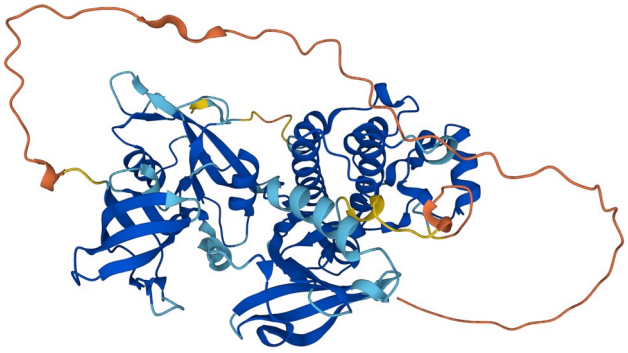

Fig. 2 Structural architecture of human LYN kinase Cartoon representation of full-length LYN (UniProt P07948) showing Src-family modules (SH4/Unique, SH3, SH2, linker, kinase). α-helices and β-sheets are indicated, with SH4/Unique largely disordered in many models. Autoinhibition and activation features are marked, and pLDDT coloring denotes model confidence. This structure provides the scaffold for mapping patient variants and interpreting domain-level signals

suggesting dosage-sensitive contributions to signaling output and plasticity [9].

In breast cancer, point mutations are relatively rare and heterogeneous in position and type (missense, occasional truncations/splice). Most single-nucleotide variants lack definitive functional annotation, and their effects likely depend on domain context (e.g., SH4/Unique vs. kinase core) and cellular compartmentalization [16].

For the majority of variants, oncogenicity remains uncertain and there is no established clinical actionability. Consequently, mapping variants to structural/functional modules and to phenotypes such as CNS metastasis may help prioritize variants for mechanistic study and clinical surveillance. Despite extensive pathway crosstalk with receptor tyrosine kinases and integrins, there are no approved *LYN*-directed therapies in breast cancer; early clinical experience with multi-target Src family kinase (SFK) inhibitors has been mixed, highlighting the importance of biomarker-guided strategies rather than unselected use [17].

CNS metastasis biology and the blood–brain barrier (BBB)

Brain metastasis proceeds through sequential bottlenecks: (i) local invasion and intravasation, (ii) survival in circulation and vascular arrest within the cerebral microvasculature, (iii) adhesion to brain endothelium and transmigration across the BBB (paracellular and/or transcellular routes), and (iv) adaptation to the neural niche, including crosstalk with astrocytes, microglia, and perivascular cells that governs early survival and outgrowth [18].

The BBB's tight junctions, low transcytosis, and specialized perivascular architecture (endothelial cells, pericytes, astrocyte end-feet) impose stringent barrier and signaling constraints on circulating tumor cells [19].

Rationale, objective, and prespecified hypotheses

Given *LYN*'s role as a membrane-proximal scaffolding kinase that integrates signals from adhesion and receptor-mediated pathways, somatic alterations in this gene warrant examination for potential relevance to metastatic patterning, including CNS involvement. Because family-wide SFK testing (*SRC*, *YES1*, *FYN*, *HCK*, *LCK*, etc.) would be underpowered and susceptible to multiplicity inflation, cross-gene comparisons are presented only as exploratory signals in the Supplement and are not interpreted under FDR-controlled frameworks.

This work provides a domain-resolved view of somatic *LYN* alterations in relation to CNS involvement in breast cancer, linking structural modules to metastatic phenotypes. By pooling harmonized, multi-cohort data and prespecifying LYN domain- and variant class–based hypotheses, we aim to generate mechanistically grounded, testable leads that prioritize biomarker development and guide functional validation.

Methods

Study design and cohort

We conducted a retrospective analysis of publicly available breast cancer cohorts accessed via cBioPortal [20–22] (download month: September 2025). All included data are de-identified and publicly released by the contributing studies; no direct interaction with human subjects occurred.

We conducted a pooled, retrospective cohort study by harmonizing breast cancer genomics and clinical annotations across 29 independent studies, yielding an analytic cohort of 5,947 unique tumors. Harmonization steps included: (i) de-duplication using stable patient/sample identifiers across portals, (ii) standardization of variant formats and clinical fields, and (iii) exclusion of records lacking essential identifiers or *LYN* coverage. Inclusion criteria were histologically confirmed breast cancer, next-generation sequencing with ascertainable *LYN* status (wild-type vs. mutant), and availability of metastatic site fields. Reporting follows STROBE recommendations for observational studies.

Exclusion criteria: duplicate or discordant records, samples failing basic quality checks, or missing essential identifiers.

Ethical conduct followed local regulations and the Declaration of Helsinki. Reporting adheres to STROBE recommendations for observational studies.

This process encompassed 33 studies totaling $n = 17{,}605$ tumors; 29 contributed NST tumors with LYN coverage to the analytic set ($n = 5{,}947$). Of these, $n = 16{,}881$ had somatic mutation profiling; applying the NST diagnosis restriction yielded $n = 14{,}050$. Within the NST set, $n = 5{,}947$ tumors (from 29 studies) had *LYN* sequenced and formed the analytic denominator for *LYN*-status

analyses. Where a study contributed multiple samples per patient, we prioritized the earliest profiled metastatic or primary specimen per patient identifier when feasible (study-specific rules documented in the analysis notebook). Cross-study duplicate patients were assessed by hashed combinations of sex/age/diagnosis year and removed when confidently identified. Study-level contributions were:

- breast_msk_2025 ($n = 1{,}566$).
- brca_tcga ($n = 980$).
- breast_ink4_msk_2021 ($n = 639$).
- breast_msk_2018 ($n = 415$).
- brca_msk_2025 ($n = 404$).
- brca_mbcproject_2022 ($n = 379$).
- brca_igr_2015 ($n = 216$).
- brca_smc_2018 ($n = 186$).
- brca_aurora_2023 ($n = 134$).
- breast_cptac_gdc ($n = 124$).
- brca_cptac_2020 ($n = 122$).
- brca_bccrc_xenograft_2014 ($n = 116$).
- brca_broad ($n = 103$).
- brca_sanger ($n = 100$).
- brca_fuscc_2020 ($n = 69$).
- brca_bccrc ($n = 65$).
- brca_mapk_hp_msk_2021 ($n = 61$).
- brca_mbcproject_wagle_2017 ($n = 61$).
- brca_pareja_msk_2020 ($n = 60$).
- brca_dfci_2020 ($n = 59$).
- bfn_duke_nus_2015 ($n = 22$).
- mbc_msk_2021 ($n = 18$).
- ilc_msk_2023 ($n = 14$).
- acbc_mskcc_2015 ($n = 12$).
- breast_alpelisib_2020 ($n = 10$).
- brca_jup_msk_2020 ($n = 5$).
- brca_hta9_htan_2022 ($n = 5$).
- brca_tcga_gdc ($n = 2$).
- brca_tcga_pan_can_atlas_2018 ($n = 1$).

Direct study links are provided in the Declarations (Availability of data and materials).

Molecular subtype and missing data policy. ER/PR/HER2 molecular subtype variables were not uniformly captured across contributing studies; HER2 status in particular was missing in the majority of tumors and often inconsistently reported between primary and metastatic specimens. We therefore prespecified that subtype variables would not be included as covariates in the primary pooled analyses, and no imputation would be attempted. Because conditioning on a partially observed determinant of CNS risk (e.g., HER2) can introduce selection bias, we also refrained from restricting the analysis to complete-case subsets.

Endpoints and variable definitions

The primary endpoint was central nervous system (CNS) metastasis at any time (yes/no), harmonized across studies using a controlled vocabulary. Metastatic sites were harmonized by mapping free-text or coded fields to a controlled vocabulary. We considered entries such as "brain", "cerebellum", "dura", "occipital", and "leptomeningeal/CSF" as CNS-positive (case-insensitive substring matching). Site fields absent were retained as missing; no imputation was performed.

Dates of CNS involvement were not systematically captured across contributing studies; therefore, baseline versus incident CNS events could not be distinguished. Time-to-event analyses (e.g., Cox or Fine–Gray) were not feasible, and we prespecified a binary "ever-CNS" endpoint without imputation of missing dates. Reported associations thus reflect odds of ever having CNS involvement in the pooled dataset rather than hazards or cumulative incidence over time.

Imaging intensity and follow-up schedules likely varied across studies; we did not adjust for follow-up time because event dates were unavailable.

Variant ascertainment and patient-level classification

Somatic *LYN* variants (coding single-nucleotide variants (SNVs) and insertions/deletions (indels)) were collected from each study's mutation tables, standardized, and collapsed to patient-level classes. Where multiple *LYN* variants occurred in the same patient, all were retained at the variant level and then collapsed to a patient-level class:

- Truncating: any nonsense, frameshift, or canonical splice-site event present (patient labeled "truncating" irrespective of co-occurring missense variants).
- Missense-only: one or more missense variants with no truncating/splice events.

Composite strings (e.g., multiple amino-acid changes) were parsed into constituent events; classification defaulted to truncating if any component met truncation criteria.

No tumors in the analytic cohort harbored more than one *LYN* variant; accordingly, no multi-hit or multi-domain collapsing was required. All observed variants had variant allele fractions (VAF) $< 50\%$, supporting single-event calls consistent with heterozygous somatic alterations rather than copy-number–driven or artifactual high-frequency events.

Domain mapping

For each variant, we extracted the codon position (when determinable) and mapped it to canonical Src-family modules: SH4/Unique (N-terminus), SH3, SH2, SH2-kinase linker, and kinase domain (activation loop noted

as a subregion within the kinase domain). Splice variants without a resolvable codon number were labeled splice; frameshifts were assigned to the position of the first impacted codon. Variants lacking a reliable position were labeled unknown for domain analyses.

Multi-hit policy. We prespecified that if a tumor harbored variants mapping to multiple domains, it would be collapsed to the most proximal domain. In this dataset, no tumors carried variants in more than one domain; thus, domain collapsing was not required.

Unknown mapping. Variants without a resolvable protein position (e.g., splice events without a defined codon, ambiguous frameshifts) were classified as "unknown domain" and excluded from domain-level tests but retained in overall LYN-mutant analyses.

Statistical analysis

For binary comparisons, we used two-sided Fisher's exact tests and reported odds ratios (ORs) with exact 95% confidence intervals. Where any cell count was zero, we additionally reported the Haldane-Anscombe corrected OR for interpretability.

Given small sample sizes, we fit a Firth bias-reduced logistic model with CNS(+) as the dependent variable and LYN mutation class (truncating vs. missense) as the covariate.

Each patient was mapped to domain presence (yes/no) for SH4/Unique, SH3, SH2, linker, and kinase domains, and per-domain Fisher's tests were conducted against CNS status. Domain-presence screens were considered hypothesis-generating; all reported p-values were Benjamini-Hochberg FDR-adjusted.

Analyses were performed in R (version 4.3.2) using stats::fisher.test and logistf packages. All tests were two-sided with $\alpha = 0.05$ unless stated otherwise. Effect sizes and their uncertainty were prioritized over thresholded significance.

To account for between-study heterogeneity in sampling and CNS ascertainment, where estimable regression models included a study fixed effect (dummy-coded). For binary comparisons, alongside pooled Fisher's exact tests, we considered Mantel–Haenszel and random-effects pooling but did not pursue formal meta-analytic estimation due to sparse per-study cells. The prespecified Firth bias-reduced logistic model was extended to include the study effect. Two-sided $\alpha = 0.05$ unless stated.

P-values and confidence intervals

Two-sided p-values for 2×2 comparisons were obtained using conditional Fisher's exact test. Alongside pooled Fisher's tests, we used a Firth bias-reduced logistic model (CNS(+) ~ truncating) and report profile penalized-likelihood 95% CIs for coefficients (reported as OR = e^β) and penalized likelihood-ratio test (LRT) p-values.

Sensitivity analyses

Sensitivity analyses included rare-variant thresholding (excluding singleton somatic *LYN* variants or those below a pre-defined frequency cut-off). For each scenario we re-fit Fisher and Firth models and report OR (95% CI) and p-values, emphasizing effect direction and precision rather than thresholded significance.

Variant-level clinical annotation

For each observed *LYN* variant, we extracted OncoKB [23, 24] (accessed 2025-09–08) annotations and integrated into the analysis workbook: oncogenicity statements (e.g., unknown oncogenic effect, likely oncogenic) and therapy notes (presence/absence of FDA-approved or compendium-listed options relevant to the alteration and disease context).

Functional enrichment

We queried STRING (Homo sapiens; accessed 2025-09–11) seeding *LYN* with active sources: experiments, databases, co-expression; minimum required interaction score ≥ 0.70. Over-representation was tested against a genome-wide background with Benjamini–Hochberg FDR. We display top non-redundant terms with $q < 0.05$.

Results

As the principal finding, the pooled analysis showed that LYN-mutated tumors had approximately six-fold higher odds of CNS metastasis compared with LYN wild type (5/46 [10.9%] vs. 110/5901 [1.9%]; OR = 6.42, 95% CI 2.49–16.56; $p = 0.0018$).

Cohort overview and ascertainment of *LYN* status

The pooled analytic cohort comprised 5,947 unique breast cancer samples from 29 independent studies after de-duplication and quality control. *LYN* status was determinable in samples where panel coverage included *LYN*; CNS metastasis was harmonized using a controlled vocabulary across studies (Fig. 3).

LYN mutation frequency and subtype-specific distribution

Across the aggregated dataset ($n = 5,947$), LYN mutations were identified in 46 tumors, corresponding to an overall prevalence of 0.77%. The remaining 5,901 cases were LYN wild type. Among the 3,584 tumors for which molecular subtype could be reliably assigned based on harmonized ER/PR, HER2, and proliferation data, LYN mutations were observed exclusively within the Luminal A/B category. No mutations were detected in HER2-enriched or triple-negative tumors, yielding a highly non-random subtype distribution.

Within this subtype-resolved subset, only eight tumors were LYN-mutated, and all eight belonged to the Luminal B subgroup. None of these eight LYN-mutant Luminal

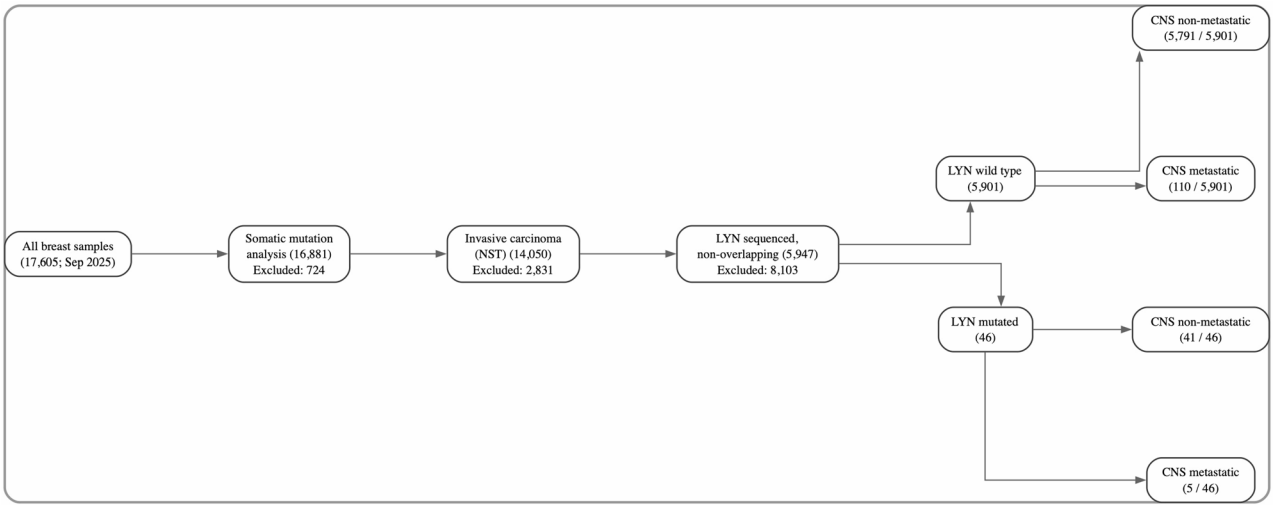

Fig. 3 Cohort assembly and analytic subsets workflow summarizing data selection from cBioPortal breast cancer studies, with inclusion restricted to invasive NST tumors having valid LYN profiling. CNS metastasis was coded as ever vs. never. Sequential exclusions illustrate the derivation of the analytic cohort

B tumors exhibited documented CNS metastasis in the harmonized dataset (0/8), consistent with the overall finding that CNS involvement does not differ significantly across molecular subgroups ($p = 0.46$).

Because subtype data are only available on a limited portion of the subcohort, subtype-specific analyses represent only a fraction of the total *LYN*-mutant cases.

Association between *LYN* mutation (present vs. WT) and CNS metastasis

In line with the principal finding summarized above, tumors harboring LYN mutations exhibited an increased occurrence of CNS metastasis relative to LYN wild-type counterparts.

In the full dataset ($n = 5{,}947$), CNS metastasis occurred in 5/46 *LYN*-mutated tumors (10.9%) versus 110/5,901 *LYN* wild-type tumors (1.9%), yielding an odds ratio = 6.42 (95% CI, 2.49–16.56) with a two-sided Fisher's exact $p = 0.0018$. This suggests a statistically significant excess of CNS involvement among *LYN*-mutant cases (Fig. 4).

Domain-resolved distribution of *LYN* mutations by CNS status

Overall heterogeneity across domains was significant (χ^2 $p \approx 0.014$), indicating that the location of the *LYN* alteration may influence CNS risk. One-versus-rest contrasts (Benjamini–Hochberg FDR control; Fig. 5):

- SH4/Unique (N-terminus): 3/3 in-domain cases were CNS-positive (100.0%), versus 2/16 in the remainder (12.5%). The 2 × 2 table contains a zero cell, yielding an infinite exact odds ratio; using a Haldane–Anscombe continuity correction for interpretability gives OR ≈ 46.2. Unadjusted $p \approx 0.010$; FDR q ≈ 0.052. For zero-cell tables, we report qualitative inference from exact testing and, for interpretability, continuity-corrected odds ratios (Haldane–Anscombe). Multiple testing for domain-level one-versus-rest contrasts used BH-FDR (UNIQUE q ≈ 0.052; others not significant).
- SH2: 0/4 in-domain CNS-positive (0.0%) versus 5/15 in the remainder (33.3%); Fisher $p \approx 0.53$. Continuity-corrected OR ≈ 0.21.
- SH3: 0/1 in-domain CNS-positive (0.0%) versus 5/18 in the remainder (27.8%); Fisher $p \approx 1.00$. Continuity-corrected OR ≈ 0.82.
- Kinase domain: 2/11 in-domain CNS-positive (18.2%) versus 3/8 in the remainder (37.5%); Fisher $p \approx 0.60$. OR ≈ 0.37.
- SH2-kinase linker: No in-domain observations; not evaluable.

Mutation class (truncating vs. missense) by CNS status

Among *LYN*-mutant cases, CNS metastasis was observed in 3/38 (7.9%) with missense variants and 2/7 (28.6%) with truncating variants. A direct Fisher's exact comparison of these class-specific rates did not reach significance (two-sided $p = 0.166$) (Fig. 6).

Framed alternatively as the proportion of truncating variants among CNS-positive vs. CNS-negative cases, the truncating share was 2/5 (40.0%) vs. 6/44 (13.6%), yielding OR = 4.22 (exact 95% CI, 0.58–30.75; two-sided Fisher $p = 0.182$). Thus, although the point estimate exceeds 1, the confidence interval is wide and includes the null under the available sample size.

In a prespecified Firth logistic model for CNS(+) ~ truncating (vs. missense) restricted to *LYN*-mutant tumors,

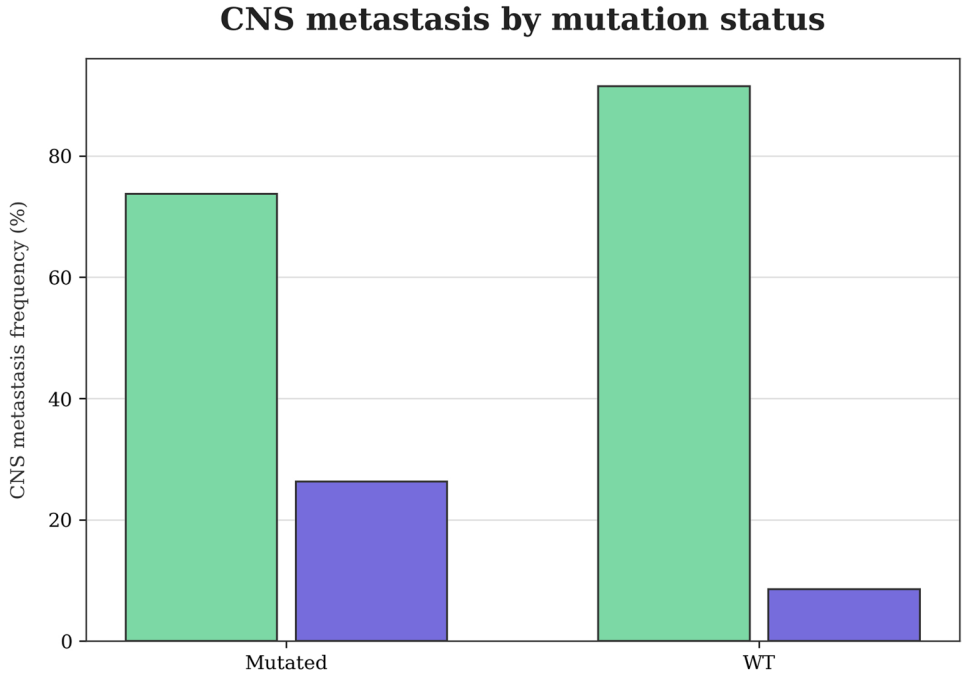

Fig. 4 CNS metastasis by LYN mutation status Comparison of CNS involvement between LYN-mutated and wild-type tumors in the pooled cohort, highlighting the increased frequency of CNS metastasis among LYN-mutated cases

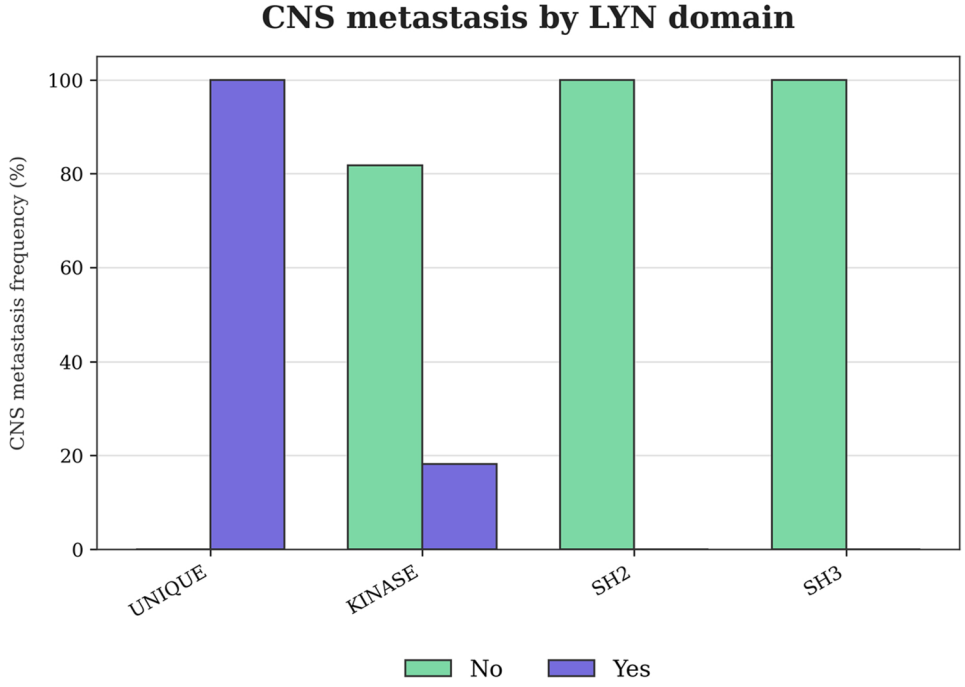

Fig. 5 CNS metastasis by LYN mutation domain Distribution of CNS-positive tumors across LYN domains (SH4/Unique, SH3, SH2, linker, kinase). Domain-specific signals are exploratory given limited mutant counts

estimates were directionally consistent with the Fisher analysis but non-significant; profile penalized-likelihood 95% CIs were wide, reflecting sparse counts (particularly truncating, $n = 7$).

Variant-level clinical annotation via OncoKB returned no oncogenic or actionable classifications for any of the observed *LYN* mutations (all annotated as 'unknown significance' or not listed), consistent with the rarity and scattered distribution of these events.

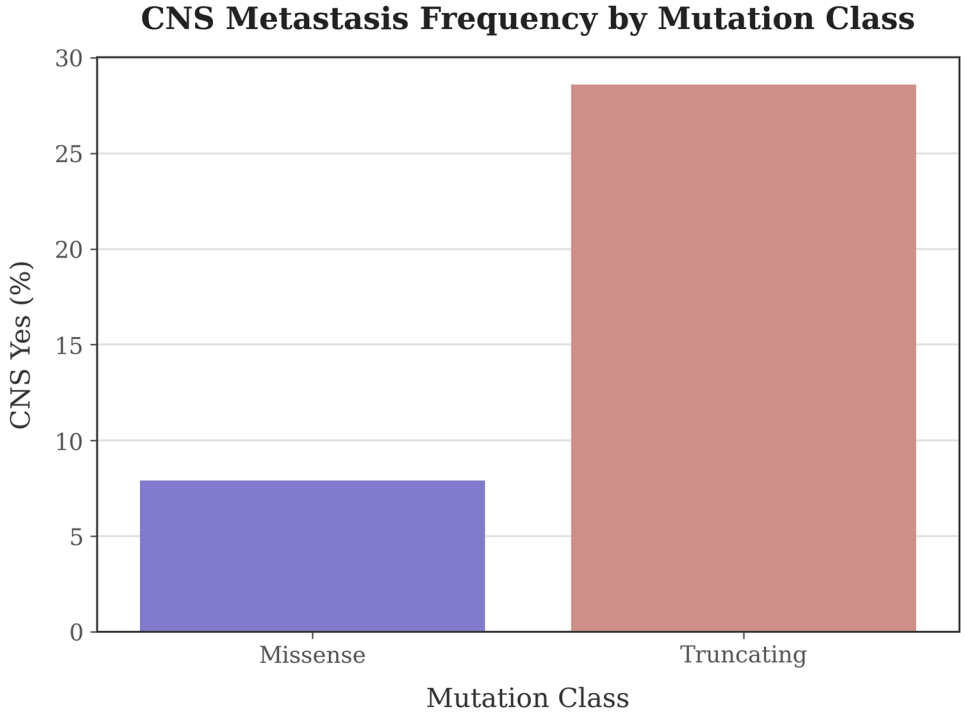

Fig. 6 CNS metastasis by LYN mutation class Comparison of CNS involvement between truncating and missense LYN-mutant tumors. Trend directionally supports higher CNS positivity in truncating variants but remains underpowered and exploratory

Discussion

Domain-specific signal as the primary biological insight

The clearest biological signal in this analysis is the preferential concentration of *LYN* alterations within the SH4/Unique region, a membrane-targeting module critical for Src-family anchoring, spatial positioning, and early integrin–FAK-mediated endothelial engagement. This localization provides a coherent mechanistic rationale for potential relevance to CNS tropism: perturbations within the SH4/Unique domain are more likely to disrupt membrane targeting, focal-adhesion turnover, and the cytoskeletal transitions required for diapedesis and blood–brain barrier interaction. In contrast, the absence of enrichment within the kinase domain—despite adequate mutational opportunity—indicates that the detectable signal does not arise from catalytic-core perturbation. This pattern aligns with established Src-family biology, in which conformational activation states and membrane-proximal signaling, rather than enzymatic potency alone, govern cross-talk with ERBB-driven and immune-modulatory pathways that influence metastatic dissemination. Taken together, the domain-specific distribution observed here positions *LYN* as a plausible contributor to adhesion–barrier circuitry rather than a classical kinase-domain effector.

Interpreting the mutation-class signal

The truncating-versus-missense comparison yielded point estimates > 1 but non-significant p values under exact testing ($p = 0.166$ for class-specific rates; $p = 0.182$ for the truncating share analysis), with wide CIs reflecting sparse truncating counts ($n = 7$) and only five CNS-positive *LYN*-mutant cases overall. These results are compatible with either a true but imprecise effect or no effect; as such, they should not be over-interpreted absent replication or larger pooled analyses and, ideally, orthogonal functional evidence.

Mechanistic considerations: *LYN*, CNS tropism, and the tumor microenvironment

LYN sits at a nodal position connecting receptor tyrosine kinases, integrins, immune receptors, and cytoskeletal scaffolds. These considerations are consistent with the membrane-targeting and adhesion–barrier framework outlined above, extending it to microenvironmental (endothelial and immune) compartments [5, 11, 12, 14, 21].

The therapeutic implications are purposely cautious. Pan-SFK inhibition has produced mixed results and may be limited by BBB penetration and pathway redundancy; conversely, domain-driven rewiring suggests combinations—e.g., SRC-family inhibitors with integrin/FAK blockade or anti-inflammatory modulators—could be more effective in biologically defined subsets [12, 19, 21]. At present, our findings are hypothesis-generating; establishing independence from canonical clinical drivers and embedding the *LYN* signal within a microenvironmental framework will require subtype-balanced, time-resolved

datasets and mechanistic validation across the tumor–endothelium–immune triad.

Contextualizing *LYN* variants within broader genomic and vascular determinants of CNS metastasis

The emerging association between LYN mutations and CNS involvement resonates with prior work highlighting the role of vascular and endothelial programs in metastatic behavior. Studies examining angiogenesis-related biomarkers in breast cancer have shown that tumors with heightened vascular remodeling signatures exhibit more aggressive dissemination phenotypes, driven in part by altered endothelial adhesion dynamics and microvascular permeability [25].

There is established clinical precedent for genotype-specific patterns of CNS involvement shaping therapeutic strategies, most prominently illustrated in EGFR-mutant non–small cell lung cancer, where the presence of activating EGFR variants predicts both an elevated propensity for CNS metastasis and responsiveness to targeted agents such as afatinib. Although LYN mutations in breast cancer are far rarer and currently lack direct clinical actionability, the analogy underscores a broader principle: even modest or infrequent somatic events can hold disproportionate relevance for CNS tropism when they interface with signaling modules governing adhesion, barrier traversal, or survival within the neural niche [26]. The present findings therefore align with a growing body of evidence that genetically defined subpopulations may harbor distinct CNS-directed metastatic trajectories, warranting prospective evaluation once larger datasets and orthogonal functional readouts become available.

Domain-specific mutational architecture has also emerged as an important dimension of genotype–phenotype relationships in hereditary and high-risk breast cancer populations. Germline sequencing studies in triple-negative breast cancer have demonstrated that pathogenic variants cluster in functionally privileged regions of BRCA1/2 and other DNA-repair genes, with domain-level patterns offering prognostic and biological resolution beyond gene-level status alone [27].

The domain-resolved approach taken in the present LYN analysis—mapping somatic variants onto SH4/Unique, SH3, SH2, and kinase modules—echoes this strategy and provides a conceptual scaffold for future mechanistic interrogation. Although our dataset is underpowered for definitive inference, the observation that CNS-positive events were directionally enriched in the membrane-targeting SH4/Unique domain is consistent with the broader notion that where within a gene a mutation resides may influence metastatic phenotypes. Larger, uniformly annotated cohorts will be essential to validate whether LYN exhibits analogous domain-specific risk architecture.

Methodological strengths

This work adheres to several practices that increase inferential robustness for rare alterations and sparse endpoints:

- Prespecified endpoint harmonization using a controlled CNS vocabulary with no imputation for missing site fields;
- Exact procedures appropriate to small cells (two-sided Fisher tests, exact/mid-P intervals where feasible) and BH-FDR control for domain screens;
- A priori domain mapping and patient-level collapsing rules;
- Multi-study pooling with de-duplication across patient/sample identifiers to reduce double counting.

Limitations

Important caveats temper interpretation. The retrospective design risks selection and information bias from clinically sequenced cohorts and free-text metastasis fields (despite normalization). The *LYN*-mutant denominator is small ($n = 46$; CNS-positive $n = 5$), yielding imprecise estimates with wide CIs and limiting multivariable adjustment. Key clinical/genomic covariates (subtype, treatment, stage, co-mutations, copy number/expression, TMB) were incompletely available, leaving residual confounding or effect modification. CNS event timing (baseline vs. follow-up) was inconsistently captured, precluding temporal inference. Finally, heterogeneity in panel coverage and site capture across studies may introduce between-study variability only partially addressed by pooled exact analyses.

From a translational standpoint, these findings should be interpreted as hypothesis-generating. *LYN* mutations are rare, clinically non-actionable, and observed effect sizes arise from small mutant denominators, limiting immediate applicability to patient management. Nevertheless, the domain-specific signal—anchored in membrane-proximal biology rather than kinase-core perturbation—provides a tractable framework for future validation in mechanistic models and larger, uniformly annotated cohorts. Until such evidence emerges, *LYN* should be viewed as a candidate component of adhesion–barrier circuitry rather than a biomarker with direct therapeutic relevance.

Consistent with this, all *LYN* variants in our dataset lacked oncogenicity or actionability classifications in OncoKB, underscoring that the signal observed here arises from exploratory phenotype mapping rather than established pathogenic annotations.

Implications and next steps

Findings suggest that domain context may be informative for assessing *LYN* variation in relation to CNS involvement; this remains exploratory. Next steps:

- External validation: Well-annotated cohorts with harmonized CNS fields and sufficient *LYN*-mut/CNS + cases to refine estimates and enable covariate-adjusted models (e.g., subtype-adjusted Firth logistic; study-stratified or random-effects meta-analysis).
- Temporal curation: Time-stamp CNS events to separate baseline from incident metastases and test lead-lag relationships with *LYN* status.
- Mechanistic studies: Isogenic models comparing SH4/Unique vs. kinase-core/regulatory-head perturbations, probing membrane targeting, endothelial adhesion, and diapedesis in reductionist and microphysiological BBB systems.
- Signaling/interactome profiling: Determine whether N-terminal alterations reprogram RTK-integrin coupling or scaffold composition to favor CNS tropism.
- Clinical pipelines: Domain-aware curation to standardize future aggregation/meta-analysis and flag putatively high-risk patterns for prospective surveillance.

Conclusion

In a harmonized, multi-study breast cancer cohort, any somatic *LYN* mutation was associated with increased odds of CNS metastasis (10.9% vs. 1.9%; OR = 6.42; 95% CI, 2.49–16.56; $p = 0.0018$). Among *LYN*-mutant tumors, domain distributions differed by CNS status, with a small-sample enrichment signal at the SH4/Unique N-terminus (FDR-borderline), while other modules did not show significant enrichment. The truncating-versus-missense comparison was directionally positive but statistically non-significant under sparse counts, and should be viewed as exploratory.

In this pooled, retrospective analysis, the observed *LYN*–CNS association should nonetheless be regarded as hypothesis-generating, given small mutant denominators and heterogeneous annotations. Putative domain-level patterns (e.g., SH4/Unique) are signal-seeking and should be interpreted as exploratory given small in-domain counts. Given the limited power and heterogeneous annotations, immediate therapeutic implications are premature, especially considering the challenges of CNS drug delivery and the mixed performance of unselected SFK inhibition.

Findings are hypothesis-generating and require independent validation in larger, uniformly annotated cohorts before any clinical application.

Abbreviations

AACR	American Association for Cancer Research
AKT	Protein Kinase B
AKT/MAPK	AKT / Mitogen-Activated Protein Kinase
BBB	Blood–Brain Barrier
BCAR1/CAS	Breast Cancer Anti-Estrogen Resistance 1 / Crk-Associated Substrate
BCR	B-Cell Receptor
BH-FDR	Benjamini–Hochberg False Discovery Rate
CD	Cluster of Differentiation
CD19	Cluster of Differentiation 19
CD22	Cluster of Differentiation 22
CD5	Cluster of Differentiation 5
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CSK	C-Terminal Src Kinase
CT	Computed Tomography
CTC	Circulating Tumor Cell
DNA	Deoxyribonucleic Acid
ECM	Extracellular Matrix
EGFR	Epidermal Growth Factor Receptor
EMT	Epithelial–Mesenchymal Transition
EPOR	Erythropoietin Receptor
ER	Estrogen Receptor
PR	Progesterone Receptor
HER2	Human Epidermal Growth Factor Receptor 2
ERBB/EGFR	ERBB Receptor Family / Epidermal Growth Factor Receptor
ERK	Extracellular Signal-Regulated Kinase
ESMO	European Society for Medical Oncology
FAK	Focal Adhesion Kinase
FDA	U.S. Food and Drug Administration
FDR	False Discovery Rate
GENIE	Genomics Evidence Neoplasia Information Exchange
GPCR	G-Protein Coupled Receptor
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
IHC	Immunohistochemistry
IL	Interleukin
IRB	Institutional Review Board
ITIM	Immunoreceptor Tyrosine-Based Inhibitory Motif
JCO	Journal of Clinical Oncology
LCK	Lymphocyte-Specific Protein Tyrosine Kinase
LYN	LYN Proto-Oncogene, Src Family Tyrosine Kinase
MAPK	Mitogen-Activated Protein Kinase
MEK	MAPK/ERK Kinase
MHC	Major Histocompatibility Complex
MPL	Myeloproliferative Leukemia Protein
NEDD9/HEF1	Neural Precursor Cell Expressed Developmentally Down-Regulated 9 / Human Enhancer of Filamentation 1
NK	Natural Killer (cell)
NST	No Special Type
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
P	Probability
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PI3K	Phosphoinositide 3-Kinase
PKC	Protein Kinase C
PLCγ	Phospholipase C Gamma
PR	Progesterone Receptor
PTEN	Phosphatase and Tensin Homolog
QC	Quality Control
qPCR	Quantitative Polymerase Chain Reaction
R	R Statistical Software
RAS	Rat Sarcoma Virus Oncogene
RHO	Ras Homolog Family
RNA	Ribonucleic Acid
ROC	Receiver Operating Characteristic
RTK	Receptor Tyrosine Kinase
SFK	Src Family Kinase

SFK/LYN	Src Family Kinases / LYN
SFK/SRC	Src Family Kinases / SRC
SFK/YES1	Src Family Kinases / YES1
SFK/FYN	Src Family Kinases / FYN
SH2	Src Homology 2 Domain
SH3	Src Homology 3 Domain
SH4	Src Homology 4 Domain
SHIP-1	SH2 Domain-Containing Inositol-5'-Phosphatase 1
SHP-1	Src Homology Region 2 Domain-Containing Phosphatase 1
SHP-2	Src Homology Region 2 Domain-Containing Phosphatase 2
SNV	Single-Nucleotide Variant
SRC	SRC Proto-Oncogene, Non-Receptor Tyrosine Kinase
STRING	Search Tool for the Retrieval of Interacting Genes/Proteins
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TJ	Tight Junction
TLR	Toll-Like Receptor
TLR2/4	Toll-Like Receptor 2 / Toll-Like Receptor 4
TMB	Tumor Mutational Burden
UNIQUE	Unique Domain (LYN N-terminal region)
WT	Wild Type
VAF	Variant Allele Fraction
CI	Confidence Interval
LRT	Likelihood-Ratio Test

Acknowledgements
We gratefully acknowledge the cBioPortal for Cancer Genomics team for providing an open platform to access and analyze cancer genomics data, and the STRING consortium for protein association networks and enrichment tools used in this study. We also thank the contributing investigators, institutions, and—most importantly—the patients—whose data made this research possible. Interpretations and conclusions are solely those of the authors and do not necessarily reflect the views of the data contributors.

Authors' contributions
E.K.Ç.: Conceptualization; Study design/Methodology; Data curation; Resources; Supervision; Writing—original draft.B.Ç.: Software; Formal analysis/Statistics; Visualization; Writing—original draft.All authors read and approved the final manuscript.

Funding
No specific funding was received for this work.

Data availability
All datasets analyzed in this study are publicly accessible from cBioPortal for Cancer Genomics. Direct study links and identifiers are provided below. We also used OncoKB for variant-level annotations and STRING for enrichment analyses; access dates are indicated.
• cBioPortal for Cancer Genomics — breast_msk_2025: https://www.cbioportal.org/study/summary?id=breast_msk_2025
• cBioPortal for Cancer Genomics — brca_tcga: https://www.cbioportal.org/study/summary?id=brca_tcga
• cBioPortal for Cancer Genomics — breast_ink4_msk_2021: https://www.cbioportal.org/study/summary?id=breast_ink4_msk_2021
• cBioPortal for Cancer Genomics — breast_msk_2018: https://www.cbioportal.org/study/summary?id=breast_msk_2018
• cBioPortal for Cancer Genomics — brca_msk_2025: https://www.cbioportal.org/study/summary?id=brca_msk_2025
• cBioPortal for Cancer Genomics — brca_mbcproject_2022: https://www.cbioportal.org/study/summary?id=brca_mbcproject_2022
• cBioPortal for Cancer Genomics — brca_igr_2015: https://www.cbioportal.org/study/summary?id=brca_igr_2015
• cBioPortal for Cancer Genomics — brca_smc_2018: https://www.cbioportal.org/study/summary?id=brca_smc_2018
• cBioPortal for Cancer Genomics — brca_aurora_2023: https://www.cbioportal.org/study/summary?id=brca_aurora_2023
• cBioPortal for Cancer Genomics — breast_cptac_gdc: https://www.cbioportal.org/study/summary?id=breast_cptac_gdc
• cBioPortal for Cancer Genomics — brca_cptac_2020: https://www.cbioportal.org/study/summary?id=brca_cptac_2020
• cBioPortal for Cancer Genomics — brca_bccrc_xenograft_2014: https://www.cbioportal.org/study/summary?id=brca_bccrc_xenograft_2014
• cBioPortal for Cancer Genomics — brca_broad: https://www.cbioportal.org/study/summary?id=brca_broad
• cBioPortal for Cancer Genomics — brca_sanger: https://www.cbioportal.org/study/summary?id=brca_sanger
• cBioPortal for Cancer Genomics — brca_fuscc_2020 (n = 69): https://www.cbioportal.org/study/summary?id=brca_fuscc_2020
• cBioPortal for Cancer Genomics — brca_bccrc: https://www.cbioportal.org/study/summary?id=brca_bccrc
• cBioPortal for Cancer Genomics — brca_mapk_hp_msk_2021: https://www.cbioportal.org/study/summary?id=brca_mapk_hp_msk_2021
• cBioPortal for Cancer Genomics — brca_mbcproject_wagle_2017: https://www.cbioportal.org/study/summary?id=brca_mbcproject_wagle_2017
• cBioPortal for Cancer Genomics — brca_pareja_msk_2020: https://www.cbioportal.org/study/summary?id=brca_pareja_msk_2020
• cBioPortal for Cancer Genomics — brca_dfci_2020: https://www.cbioportal.org/study/summary?id=brca_dfci_2020
• cBioPortal for Cancer Genomics — bfn_duke_nus_2015: https://www.cbioportal.org/study/summary?id=bfn_duke_nus_2015
• cBioPortal for Cancer Genomics — mbc_msk_2021 https://www.cbioportal.org/study/summary?id=mbc_msk_2021
• cBioPortal for Cancer Genomics — ilc_msk_2023: https://www.cbioportal.org/study/summary?id=ilc_msk_2023
• cBioPortal for Cancer Genomics — acbc_mskcc_2015: https://www.cbioportal.org/study/summary?id=acbc_mskcc_2015
• cBioPortal for Cancer Genomics — breast_alpelisib_2020: https://www.cbioportal.org/study/summary?id=breast_alpelisib_2020
• cBioPortal for Cancer Genomics — brca_jup_msk_2020: https://www.cbioportal.org/study/summary?id=brca_jup_msk_2020
• cBioPortal for Cancer Genomics — brca_hta9_htan_2022: https://www.cbioportal.org/study/summary?id=brca_hta9_htan_2022
• cBioPortal for Cancer Genomics — brca_tcga_gdc: https://www.cbioportal.org/study/summary?id=brca_tcga_gdc
•cBioPortal for Cancer Genomics — brca_tcga_pan_can_atlas_2018: https://www.cbioportal.org/study/summary?id=brca_tcga_pan_can_atlas_2018
Other resources:
OncoKB — https://www.oncokb.org/ (accessed 2025-09-08)
STRING — https://string-db.org/ (accessed 2025-09-11)

Declarations

Ethics approval and consent to participate
This study analyzed only publicly available, de-identified data aggregated from multiple studies and portals. There was no interaction with human participants and no access to identifiable private information. In accordance with applicable regulations and institutional policies, this secondary analysis of de-identified public data is not considered human subjects research; institutional review board oversight and informed consent were not required. Reporting follows STROBE.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pathology, Afyonkarahisar State Hospital, Afyonkarahisar, Turkey
[2]System Biotechnology Advance Research Unit, Biotechnology Institute, Ankara University, Tandogan, Ankara, Turkey
[3]Department of Nuclear Medicine, Afyonkarahisar State Hospital, Afyonkarahisar, Turkey

Received: 12 September 2025 / Accepted: 26 November 2025
Published online: 05 December 2025

References

1. Raghavendra AS, Ibrahim NK. Breast cancer brain metastasis: a comprehensive review. JCO Oncol Pract. 2024;20(10):1348–59.
2. Stavrou E, Winer EP, Lin NU. How we treat HER2-positive brain metastases. ESMO Open. 2021;6(5):100256.
3. Boire A, Brastianos PK, Garzia L, Valiente M. Brain metastasis. Nat Rev Cancer. 2020;20(1):4–11.
4. Soung YH, Clifford JL, Chung J. Crosstalk between integrin and receptor tyrosine kinase signaling in breast carcinoma progression. BMB Rep. 2010;43(5):311–8.
5. Han J, Zhang G, Welch EJ, Liang Y, Fu J, Vogel SM, et al. A critical role for Lyn kinase in strengthening endothelial integrity and barrier function. Blood. 2013;122(25):4140–9.
6. Tornillo G, Knowlson C, Kendrick H, Cooke J, Mirza H, Aurrekoetxea-Rodríguez I et al. Dual Mechanisms of LYN Kinase Dysregulation Drive Aggressive Behavior in Breast Cancer Cells. Cell Rep. 2018;25(13):3674-92.e10.
7. Parsons SJ, Parsons JT. Src family kinases, key regulators of signal transduction. Oncogene. 2004;23(48):7906–9.
8. Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Res. 2023;51(D1):D638-d46.
9. Choi YL, Bocanegra M, Kwon MJ, Shin YK, Nam SJ, Yang JH, et al. LYN is a mediator of epithelial-mesenchymal transition and a target of dasatinib in breast cancer. Cancer Res. 2010;70(6):2296–306.
10. Safran M, Rosen N, Twik M, BarShir R, Stein TI, Dahary D, et al. The genecards suite. In: Abugessaisa I, Kasukawa T, editors. Practical guide to life science databases. Singapore: Springer Nature Singapore; 2021. pp. 27–56.
11. Doron H, Pukrop T, Erez N. A blazing landscape: neuroinflammation shapes brain metastasis. Cancer Res. 2019;79(3):423–36.
12. Wheeler SE, Morariu EM, Bednash JS, Otte CG, Seethala RR, Chiosea SI, et al. Lyn kinase mediates cell motility and tumor growth in EGFRvIII-expressing head and neck cancer. Clin Cancer Res. 2012;18(10):2850–60.
13. Okada M. Regulation of the SRC family kinases by Csk. Int J Biol Sci. 2012;8(10):1385–97.
14. Sicheri F, Moarefi I, Kuriyan J. Crystal structure of the Src family tyrosine kinase Hck. Nature. 1997;385(6617):602–9.
15. Boggon TJ, Eck MJ. Structure and regulation of Src family kinases. Oncogene. 2004;23(48):7918–27.
16. Koboldt DC, Fulton RS, McLellan MD, Schmidt H, Kalicki-Veizer J, McMichael JF, et al. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61–70.
17. Zhang S, Yu D. Targeting Src family kinases in anti-cancer therapies: turning promise into triumph. Trends Pharmacol Sci. 2012;33(3):122–8.
18. Wang Y, Ye F, Liang Y, Yang Q. Breast cancer brain metastasis: insight into molecular mechanisms and therapeutic strategies. Br J Cancer. 2021;125(8):1056–67.
19. Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. Nat Rev Cancer. 2020;20(1):26–41.
20. de Bruijn I, Kundra R, Mastrogiacomo B, Tran TN, Sikina L, Mazor T, et al. Analysis and visualization of longitudinal genomic and clinical data from the AACR Project GENIE Biopharma Collaborative in cBioPortal. Cancer Res. 2023;83(23):3861–7.
21. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal. 2013;6(269):pl1.
22. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012;2(5):401–4.
23. Suehnholz SP, Nissan MH, Zhang H, Kundra R, Nandakumar S, Lu C, et al. Quantifying the expanding landscape of clinical actionability for patients with cancer. Cancer Discovery. 2024;14(1):49–65.
24. Chakravarty D, Gao J, Phillips S, Kundra R, Zhang H, Wang J et al. OncoKB: A precision oncology knowledge base. JCO Precision Oncol. 2017 (1):1–16.
25. Abbasi-Dokht T, Malek F, Nafissi N, Mohammadlou M, Sheikh M, Akbari S, et al. Assessing angiogenesis factors as prognostic biomarkers in breast cancer patients and their association with clinicopathological factors. Biomarkers. 2024;29(1):36–43.
26. Van Pham T, Vu TH, Nguyen HTT, Pham PC, Do AT, Nguyen TK, et al. The effectiveness of Afatinib as first-line treatment in Vietnamese patients with EGFR-mutant non-small cell lung cancer and brain metastases. Asia Pac J Clin Oncol. 2025;21(3):281–9.
27. John J, Bapat A, Gahlaut S, Luke N, Kumar R, Thakur Y, et al. Assessing germline mutational profile and its clinicopathological associations in Triple Negative Breast Cancer. Cancer Genet. 2025;296-297:65-75.

Publisher's Note