基於靶向定序的乳癌 ERBB2、ERBB3、ESR1 與 PIK3CA 突變圖譜探索

Exploration of the Mutation Landscape of *ERBB2*, *ERBB3*, *ESR1*, and *PIK3CA* in Breast Cancer Based on Targeted Sequencing

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Introduction

Background

Breast cancer has recently surpassed lung cancer as the most common cancer worldwide, according to the World Health Organization. In Taiwan, it is the leading cancer among women, with the age-standardized incidence rate doubling between 1997 and 2016, and it currently ranks first in incidence and third in mortality among Taiwanese females[1].

Previous studies in Taiwanese breast cancer patients reported that 66% of cases harbored at least one actionable alteration, with the most frequent mutations occurring in *PIK3CA* (38%), *ERBB2* (23%), and *ESR1* (10%), while less common variants included *ERBB3* (<5%)[2]. Guided by these findings, we focused on four clinically relevant genes: *PIK3CA*, *ERBB2*, *ERBB3*, and *ESR1*. *PIK3CA* mutations are associated with the efficacy of PI3K inhibitors; *ERBB2* (HER2) is a well-established therapeutic target; *ERBB3* may modulate HER2 signaling; and *ESR1* hotspot mutations are linked to endocrine therapy resistance. Examining these genes provides clinically meaningful insights into the mutation landscape of Taiwanese breast cancer patients[3].

Targeted sequencing using next-generation sequencing (NGS) allows high-resolution analysis of cancer-associated genes. In particular, circulating tumor DNA (cfDNA) offers a minimally invasive source for mutation detection and disease monitoring. Despite the growing evidence, data on these mutations in Taiwanese patients remain limited, highlighting the need for further investigation.

Research Objective

This study summarizes the mutation landscape of a single-institution Taiwanese cohort of 71 breast cancer patients using targeted sequencing data, visualized with OncoPrinter and Mutation Map. We focused on clinically relevant genes such as *ESR1*, *PIK3CA*, *ERBB2*, and *ERBB3*, providing preliminary descriptive observations as a foundation for future larger-scale studies.

Methdology

Patients and Samples

A total of 71 breast cancer samples were collected from 71 patients, including 43 tissue-derived samples from stage I–III patients (analyzed using the TSO500 panel) and 28 plasma-derived samples from stage IV patients (cfDNA).

Sequencing Platform

Next-generation sequencing (NGS) was performed using Illumina-based targeted panels (TruSight Oncology and Amoy panels) to detect somatic alterations.Targeted sequencing was performed using the Illumina TruSight Oncology 500(TSO500) panel, covering cancer-associated genes with known clinical relevance.

Data Processing and Analysis

Data were processed through standard bioinformatics pipelines. For this study, we focused on *PIK3CA*, *ERBB2*, *ERBB3*, and *ESR1* due to their clinical significance in breast cancer therapy and resistance mechanisms.

Mutations were annotated for functional impact and oncogenic potential. Mutation distributions were summarized and visualized using OncoPrinter and MutationMap. Additional annotations and visualizations of variants were performed using the OncoKB database and cBioPortal, which are based on PierianDx-generated reports [4,5].

References

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[3] Bertucci F, Ng CKY, Patsouris A, et al. Genomic characterization of metastatic breast cancers. Nature. 2019;569:560–564. doi:10.1038/s41586-019-1057-1
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Results

(**Figure 1**) **Tissue cohort (TSO500, stage I–III)**: No recurrent oncogenic SNVs or indels were identified; only copy number changes, including shallow deletions and focal gains, were detected.

(**Figure 2**) **Plasma cohort (cfDNA, stage IV)**: Samples from metastatic patients harbored multiple oncogenic mutations, including hotspot variants in *PIK3CA*, *ESR1*, *ERBB2*, and *ERBB3* (**Table 1**).

Gene	Mutation frequency
ESR1	25% (7/28)
PIK3CA	25% (7/28)
ERBB2	4.6% (1/28)
ERBB3	4.6% (1/28)

Table 1. Summary of mutation frequencies

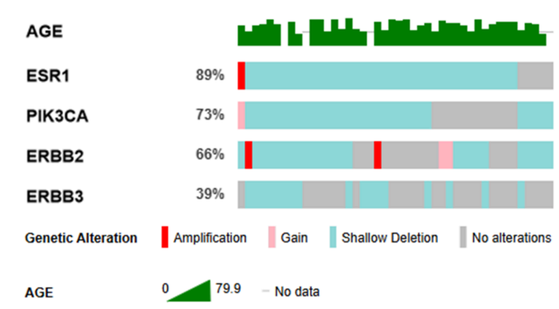

Figure 1.

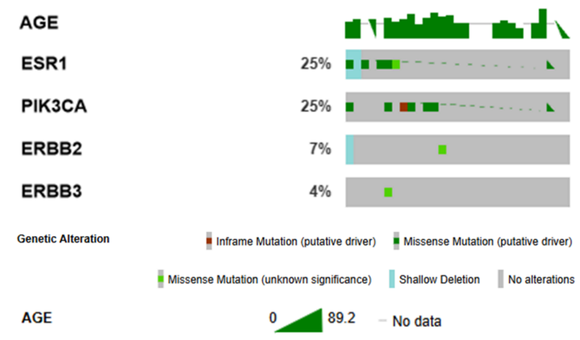

Figure 2.

To further characterize the distribution of hotspot variants, we generated lollipop plots for the most frequently altered genes, *PIK3CA* and *ESR1*.

(**Figure 3**) Hotspot mutations (Y537C, D538G) are located in the ligand-binding domain (LBD). These mutations are oncogenic and lead to ligand-independent receptor activation. Clinically, they are associated with resistance to endocrine therapies such as tamoxifen and fulvestrant. *ESR1* mutations are enriched in hormone receptor–positive, advanced breast cancer.

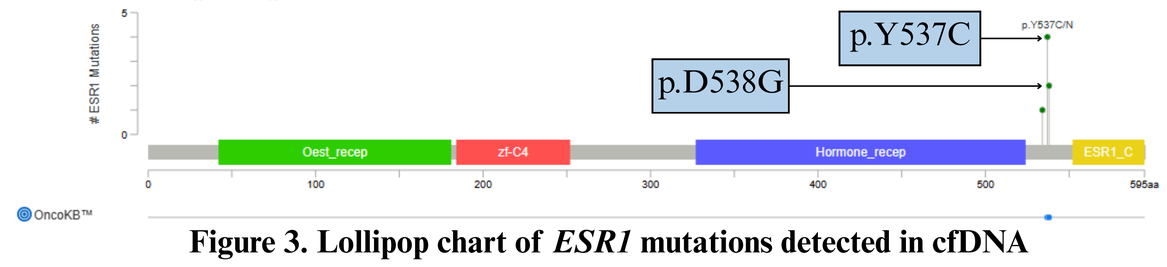

Figure 3. Lollipop chart of *ESR1* mutations detected in cfDNA

(**Figure 4**) In our cfDNA cohort, the most frequent *PIK3CA* hotspot was H1047R (kinase domain), followed by E453Q (C2 domain). Classic helical-domain hotspots E542K/E545K were present at lower frequencies, possibly due to limited sample size. These variants are oncogenic and activate the PI3K/AKT/mTOR pathway, supporting the clinical relevance of PI3K inhibitor therapy (e.g., alpelisib, in HR+/HER2– advanced breast cancer). One in-frame deletion in *PIK3CA* was also detected.These mutations are frequently observed across multiple cancer types, with breast cancer being one of the most enriched .

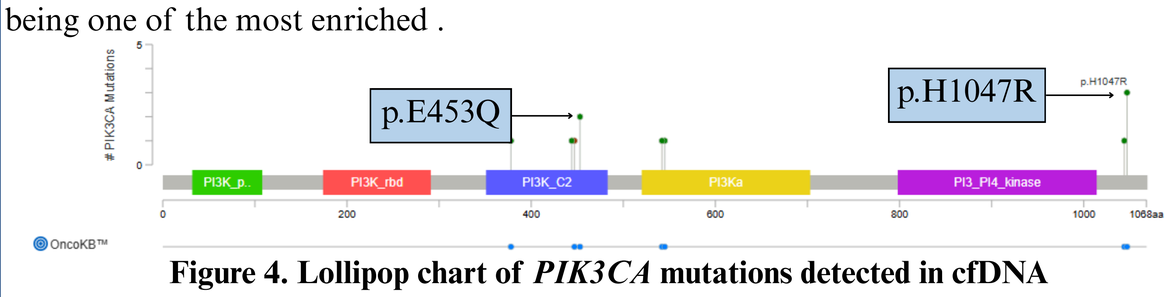

Figure 4. Lollipop chart of *PIK3CA* mutations detected in cfDNA

Discussion and Conclusion

Despite the limited sample size, the mutation landscape we observed is consistent with previous reports and underscores the potential clinical importance of these genes. These findings further support their clinical relevance in Taiwanese patients.

- ***PIK3CA*** mutations remain the most frequent and actionable, supporting the relevance of *PI3K*-targeted therapies.
- ***ESR1*** mutations suggest possible endocrine resistance, warranting further investigation in Taiwanese populations.
- ***ERBB2*/*ERBB3*** alterations, though less frequent, reinforce their role as therapeutic targets and signaling partners in breast cancer biology.

Notably, most actionable mutations in our cohort were detected in cfDNA from stage IV patients, whereas early-stage tissue samples showed only shallow deletions and gains. This aligns with the greater heterogeneity and mutation burden typically seen in advanced tumors, and also highlights the clinical value of cfDNA as a liquid biopsy, particularly in the metastatic setting. Our observation of frequent shallow deletions may reflect either technical aspects of cfDNA sequencing or biological tumor diversity, warranting further validation in larger cohorts.