

Hybrid High-Depth Plasma Fragmentomics Improves EGFR Classification in Non-Small Cell Lung Carcinoma

Tien-Dung Bui, Yung-Feng Lin, Chao-Hua Chiu, Shih-Feng Tsai, Nguyen-Quoc-Khanh Le, Teh-Ying Chou

INTRODUCTION

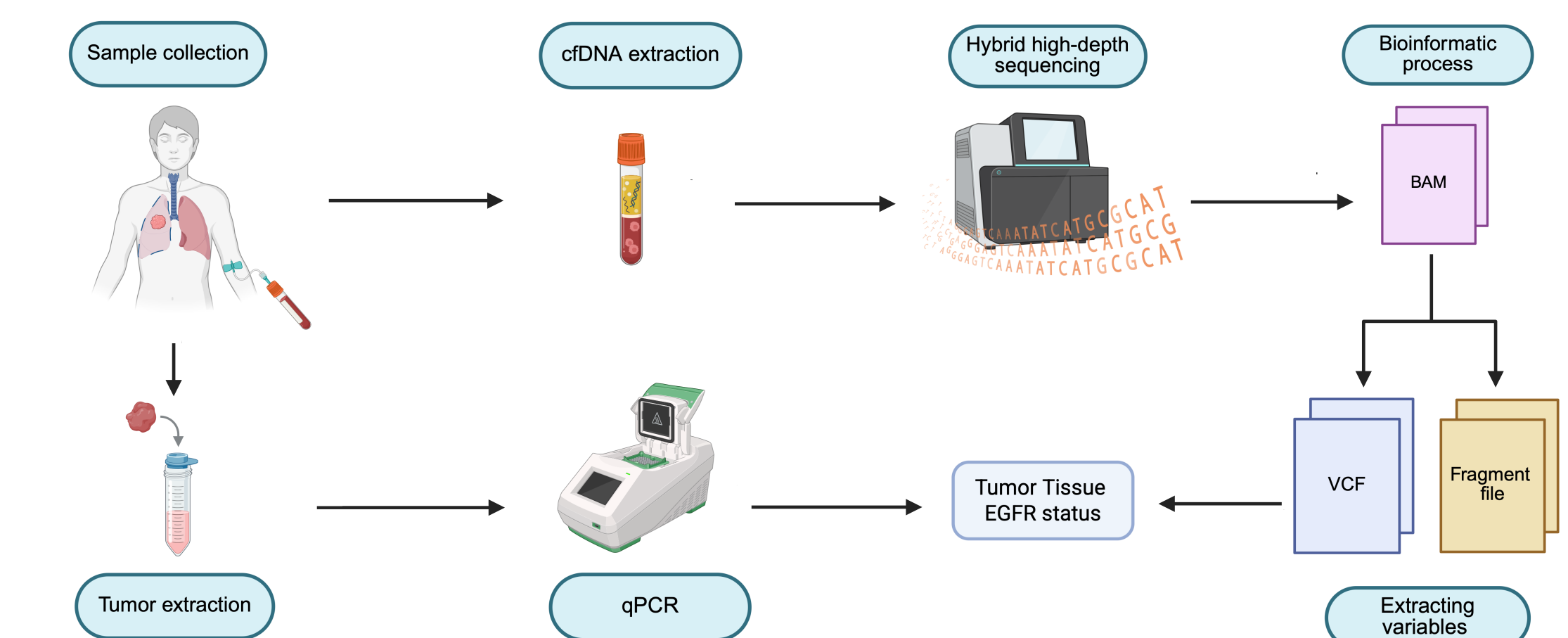
- Plasma cfDNA EGFR genotyping is widely used in NSCLC, but false-negative plasma results remain clinically important.
- Fragmentomic features embedded in high-depth plasma sequencing may provide complementary information beyond conventional variant calling.
- Objective:** To determine whether hybrid high-depth plasma fragmentomics improves tissue EGFR classification and identifies missed positives among plasma VCF-negative patients.

CONCLUSION

- Integrating plasma fragmentomics with conventional plasma variant calling improved tissue EGFR classification.
- Fragmentomics partially rescued tissue-positive cases among plasma VCF-negative patients.
- Fragmentomics provides complementary information beyond conventional plasma variant calling from the same sequencing data.

METHODS

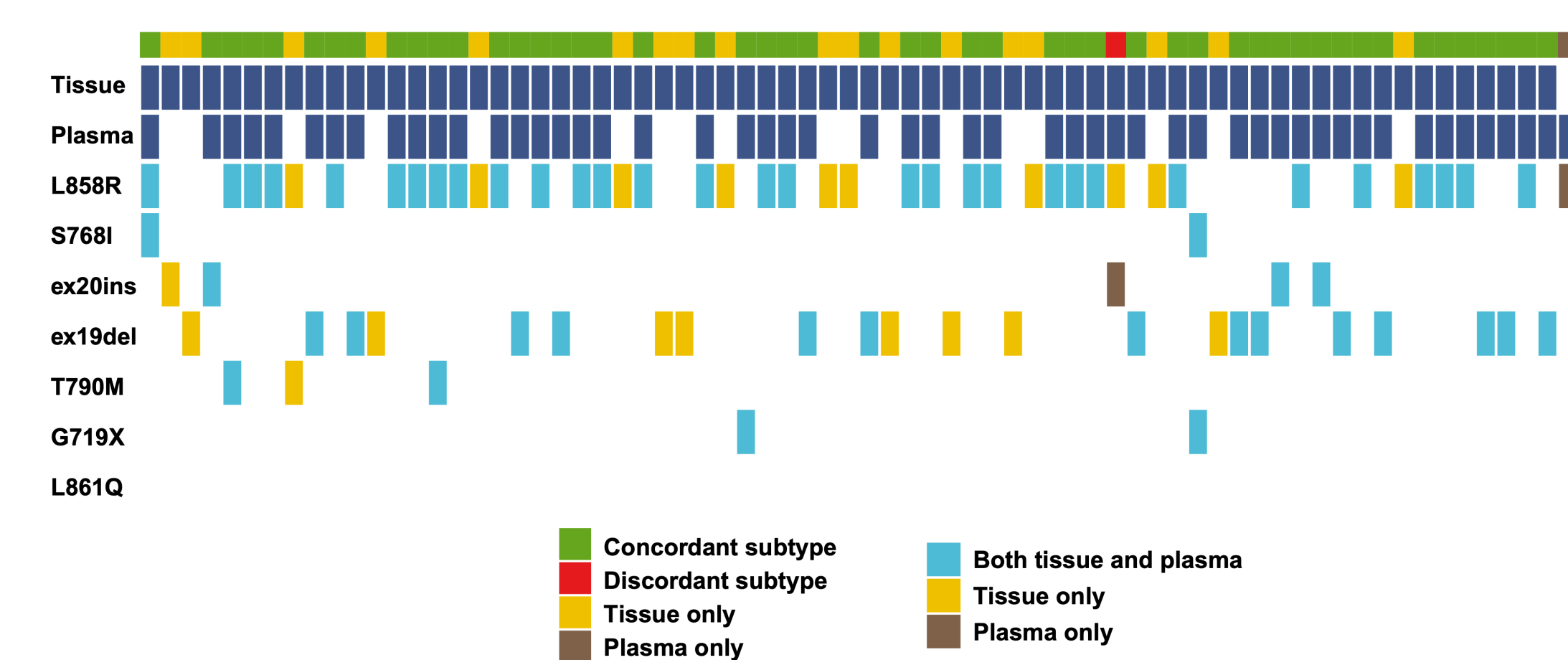
- Cohort:** 146 patients with paired tissue EGFR testing and plasma cfDNA hybrid high-depth sequencing.
- Fragmentomics:** Features derived from targeted-panel and WES-only regions.
- Models:** VCF-only, fragmentomics-only, and combined VCF + fragmentomics.
- Evaluation:** Repeated stratified 5-fold cross-validation with out-of-fold predictions. ROC-AUC, AP, and FPR ≤ 0.05 .



RESULTS

3.1 Plasma–tissue EGFR concordance

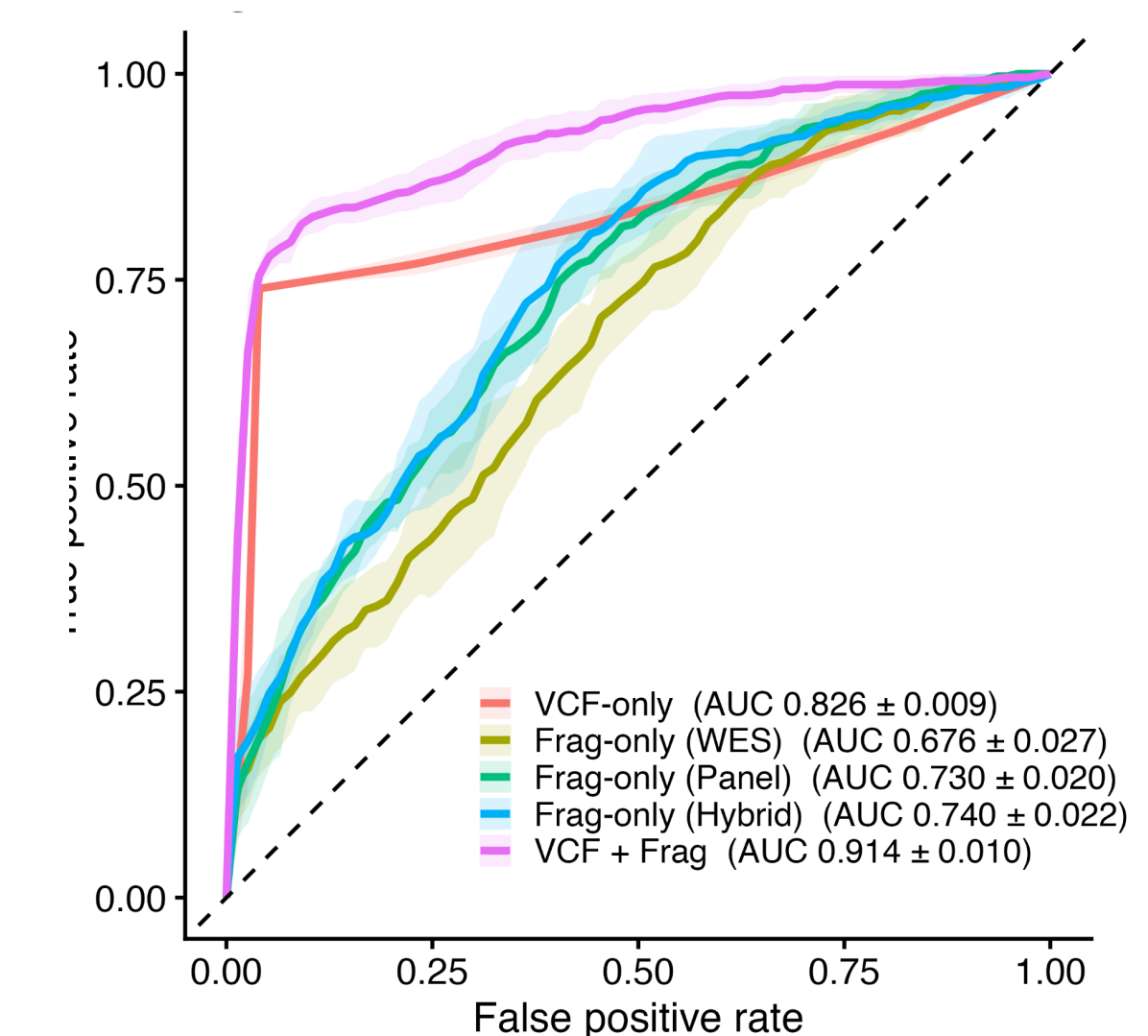
Plasma VCF showed high specificity but missed a clinically relevant subset of tissue EGFR-positive cases.



Plasma VCF achieved a sensitivity of 0.739 and specificity of 0.961, with 18/69 (26.1%) tissue EGFR-positive cases remaining plasma VCF-negative.

3.2 EGFR classification performance

The combined VCF + fragmentomics model achieved the best overall discrimination. VCF-only achieved an AUC of 0.826 ± 0.009 , whereas combining with fragmentomics improved performance to an AUC of 0.914 ± 0.010 .



3.3 Rescue analysis

In the plasma VCF-negative subgroup, fragmentomics-guided triage rescued 5.3 ± 1.16 of 18 missed tissue-positive cases at FPR ≤ 0.05 and 5.6 ± 0.70 of 18 under a top-10% call-rate policy.