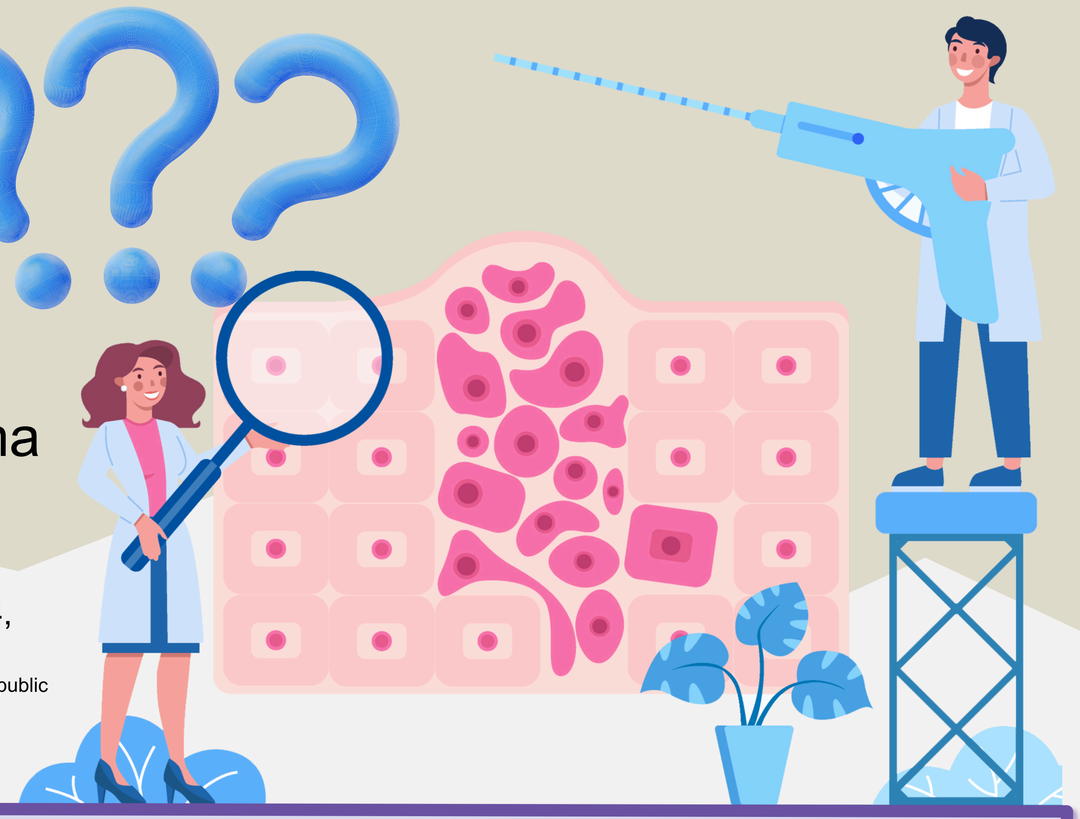
One for all...

Morphology-resolved search for mutations in non-responders to anti-EGFR therapy in colorectal carcinoma



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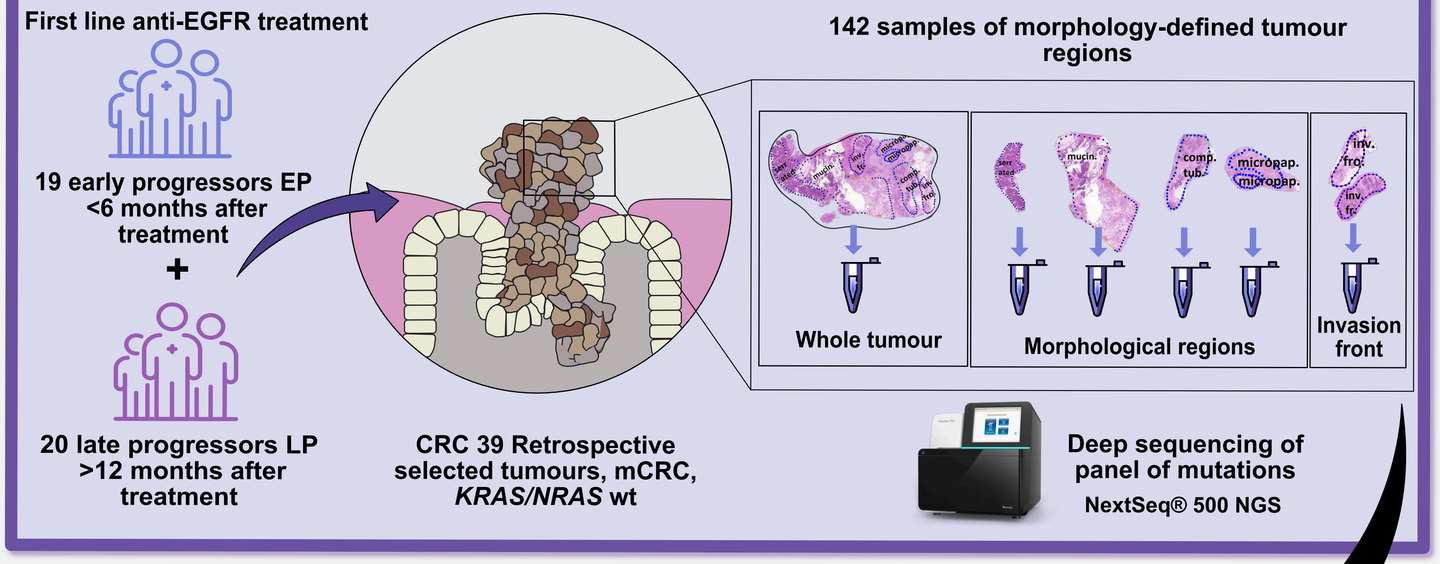
Introduction

- **Metastatic CRC (mCRC) carries a poor prognosis, with a 5-year survival rate below 15%.**
- **While EGFR-targeted therapy has shown some efficacy, resistance often develops, limiting its duration of effectiveness to 8-10 months in responsive patients.**
- **Tumor heterogeneity further complicates treatment, with intratumoral heterogeneity (ITH) impacting molecular assessments and treatment outcomes.**

Our study investigates whether rare genomic abnormalities, detectable only regionally, could predict shorter time-to-progression in CRC.

Methods



RESULTS

Tumours from the EP group exhibited a higher mutational burden including with key biological processes.

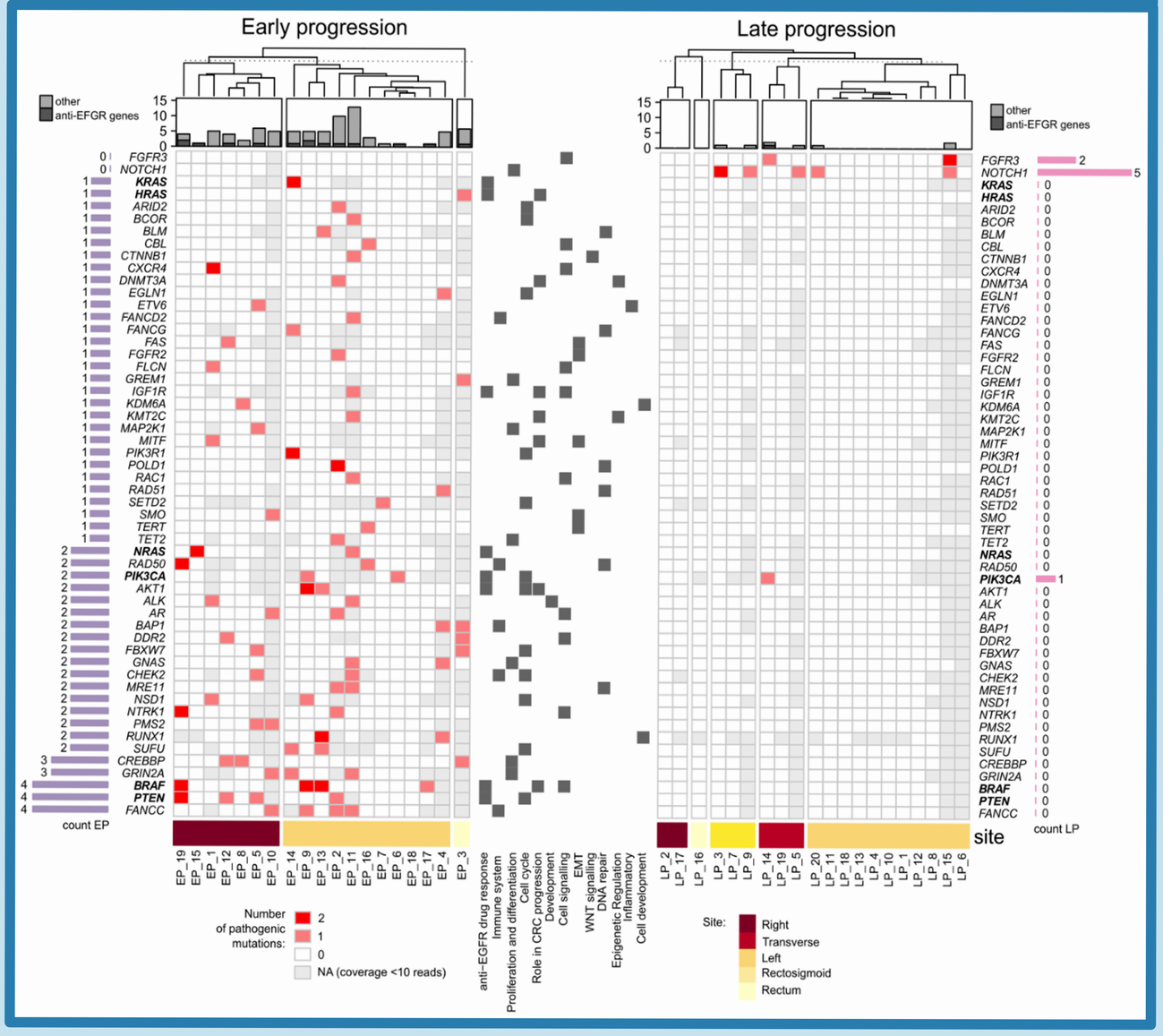


Figure 1. Presence of any pathogenic mutations in genes known for their role in anti-EGFR therapy response and in other genes specific for the early progressing or late progressing group.

The intratumor heterogeneity influenced the identification of mutations associated with anti-EGFR therapy.

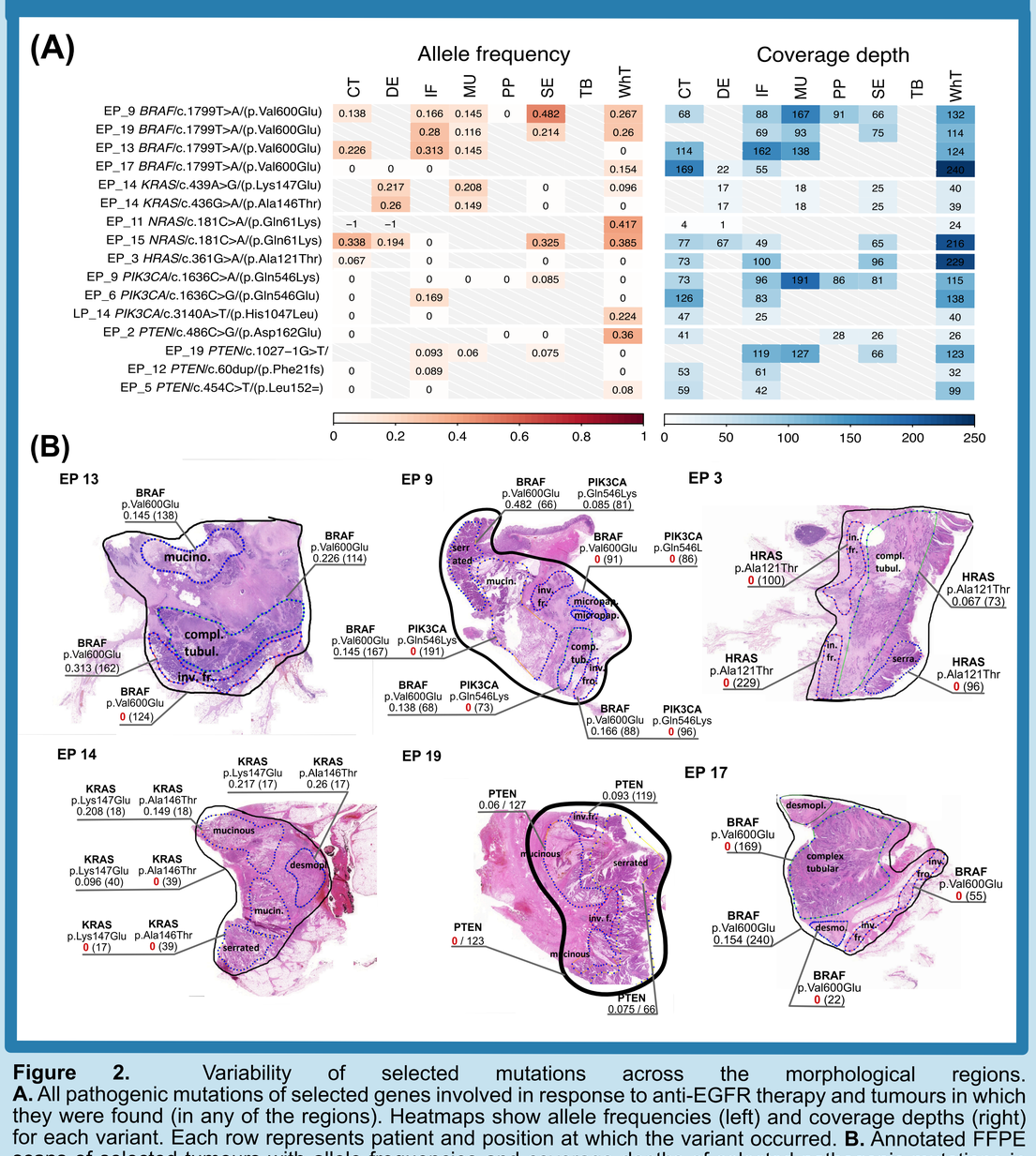


Figure 2. Variability of selected mutations across the morphological regions. **A.** All pathogenic mutations of selected genes involved in response to anti-EGFR therapy and tumours in which they were found (in any of the regions). Heatmaps show allele frequencies (left) and coverage depths (right) for each variant. Each row represents patient and position at which the variant occurred. **B.** Annotated FFPE scans of selected tumours with allele frequencies and coverage depths of selected pathogenic mutations in genes implicated in anti-EGFR therapy response.

CONCLUSION

- Early progressing (EP) tumors exhibited a higher mutational burden compared to late progressing (LP) tumors, indicating genetic complexity and aggressiveness, with mutations in genes like KRAS, BRAF, NRAS, HRAS, PTEN, and PIK3CA.
- Mutational profiles varied across morphological regions within tumors, impacting therapeutic strategies and treatment responses. Inaccurate identification of RAS/RAF mutations can result from inappropriate tumor block selection and intra-tumor heterogeneity (ITH), highlighting the need for detailed sampling and improved assessment methods.
- PIK3CA exon 20 mutations and PTEN alterations may reduce anti-EGFR mAb responsiveness, but their clinical applicability remains uncertain due to challenges in assessment and sampling sensitivity.

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