00340 A Novel 16-gene Panel Assay to Characterise and Profile Breast Fibroepithelial Lesions - A Potential Adjunctive Diagnostic Tool

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Aims: Breast fibroepithelial lesions (FELs) are a heterogenous group of biphasic neoplasms that include the common fibroadenomas (FAs) to the rarer phyllodes tumours (PTs). Diagnosing breast FELs on core biopsy specimens is challenging due to limited tissue availability, inter-observer variability, overlapping histological features and tumour heterogeneity. As therapeutic surgical options hinge on the histological diagnosis, a novel 16-gene panel assay was developed to help improve the accuracy of the preoperative diagnosis on core biopsy specimens.

Methodology: DNA extraction and targeted sequencing using our customized 16-gene panel were performed on 275 formalin-fixed, paraffin-embedded (FFPE) breast FEL specimens, collected from 2008-2012 at the Singapore General Hospital. A model was developed through machine learning to assist in discriminating the FELs across the spectrum.

Result: A total of 167 FAs, 24 benign, 14 borderline and 6 malignant PTs, were successfully profiled. Mutations in all 16 genes were observed across the FELs, except for the lack of PTEN mutations in FAs; MAP3K1 and IGF1R mutations in PTs. In the PTs, significantly higher mutation rates were observed in the TERT promoter ($p<0.0001$), RARA ($p<0.0001$), FLNA and TP53 ($p=0.020$ and 0.018, respectively) genes. In addition to the higher mutation burden seen in PTs ($p<0.0001$), TERT promoter ($p<0.0001$), frameshift, nonsense and splice site ($p=0.001$, 0.0004 and 0.043, respectively) mutations were also more likely to be associated with the PTs. Machine learning has identified 7 important genes (MED12, KMT2D, SETD2, TERT, RARA, RB1 and TP53) in differentiating the FELs.

Conclusion: This novel study demonstrates the ability to extract DNA of sufficient quality and quantity for targeted sequencing from FFPE core biopsy specimens, along with the successful characterisation and profiling of them using our customized 16-gene panel. A prognostic scoring system has been modeled on our 16-gene panel assay, with larger numbers required to validate this as an adjunctive diagnostic tool in clinical practice.