Genomic atlas of oral leukoplakia during the transition to oral squamous cell carcinoma for biomarker identification

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Head and neck cancer is the sixth most prevalent malignancy worldwide with over 10,000 death per year in the United States alone. The main risks for developing head and neck cancer are tobacco exposure, alcohol consumption, and human papilloma virus (HPV) infection. Oral cavity squamous cell carcinoma (OSCC) encompasses the majority of all oral cancers and is the most predominant subtype of HPV-negative head and neck cancer. OSCCs are often preceded by oral potentially malignant disorders with oral leukoplakias (OL) being the most common precursor lesion. In this project, our primary goal is to evaluate the evolutionary role of somatic mutations in the transition from OL into OSCC to develop actionable biomarkers by compressively profiling over 300 pairs OL and OSCC. Here, we present a pilot of the project where we examine whole-exome sequencing data and whole-genome sequencing data from 29 OSCCs and 35 OLs from two cohorts respectively: (*i*) an India cohort encompassing 28 paired OSCC and OL; and (*ii*) a Taiwan cohort including 1 OSCC and 7 OL cases. Molecular events were identified by using our previously developed bioinformatics pipelines to reveal: (*i*) driver genes, (*ii*) tumor mutation burden, (*iii*) mutational signatures, (*iv*) tumor clonality, and (*v*) copy number alterations. Amongst the 28 Indian cases, the top three most mutated driver genes were *CASP8* (9/28 samples), *TP53* (2/28), and *PIK3CA* (2/28). Further, the median tumor coding mutation burden (TMB) per Mb for OSCC was 5.43, whereas the TMB for OL was 2.12 (p-value 0.01). Genes that were significantly mutated in OSCC but not OL samples were *TP53* and *FBXW7* (Fisher Exact Test's p-values < 0.05). While comparing oral cancer samples between the India and Taiwan cohort, *HRAS* and *NOTCH1* were not among the top 30 mutated genes in the Taiwanese cohort. Taken together, when combined with AI approaches, this study will allow the development of molecular biomarkers for differentiating OLs that are benign from ones that will progress to OSCC as well as provide opportunities to design targetable interventions which can likely halt the malignant transition.

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