Molecular epidemiological analysis of oral cancer in the Indian population reveals region-specific differences in the spectrum of driver mutations and oncogenic pathways

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Oral and lip cancer have the third highest incidence and mortality among men and women in India. Risk of oral cancer is significantly increased by the use of tobacco, alcohol and HPV infection. In India, certain regions in the country have a higher incidence of oral cancer compared to other regions, and factors contributing to these differences remain unknown. We set out to examine the molecular basis of region-specific differences by profiling four distinct oral cancer cohorts collected from the Northern, Eastern, Southern and Western regions of the country. We selected cohorts that maximized the probability that all individuals shared similar environmental and lifestyle factors within a given region. In addition, we collected samples of tongue and buccal lesions to investigate factors that predisposed an individual to one cancer and not the other, even if they came from the same geographical area. Our analysis shows that there are common driver mutations in *TP53*, *CASP8*, *PIK3CA*, *NOTCH1*, *HRAS* and *MLL2* genes across samples from different regions. In addition, we also identified a large number of potentially pathogenic novel alterations that were enriched in samples from certain regions in the country. To gain further insight, we profiled the tumor microenvironment from RNA-seq data and identified immune and stromal signatures that correlated with alterations in driver genes and oncogenic pathways. Analysis of tumor neo-antigens using our proprietary analysis platform identified common and unique T-cell neo-epitopes in buccal and tongue cancers. By combining the immune and the stromal signatures with potential T-cell neo-epitopes in each sample, we developed a predictive score of response to immuno-oncology therapies.