## Genetic susceptibility and fine-mapping of human leukocyte antigen loci in head and neck cancer

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Head and neck cancer (HNC) is the sixth most common cancer worldwide originating from oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx causing 444,347 deaths in 2020. Although alcohol, tobacco, and human papillomavirus (HPV) are major risk factors for HNC, only a small fraction of high-risk individuals developed HNC implying a crucial role of genetic susceptibility in the disease etiology.

In 2014, Genome-Wide Association Study (GWAS) was performed with 2,398 individuals with laryngeal squamous cell carcinoma cases and 2,804 cancer-free controls from Chinese populations, and identified a novel susceptibility loci in complex human leukocyte antigen (HLA), which plays crucial role in immune response. Subsequently, two separate GWASs has been conducted and consistently identified locus in HLA region in association with HNC. Recently, this signal of HLA region was confirmed to be specific to HPV(+) in oropharyngeal cancer suggesting the role of HLA variants in the immune pathogenesis. Despite these significant findings, it is important to note that imputed data for the HLA locus may pose challenges due to high level of linkage disequilibrium and polymorphism. Thus, fine-mapping studies for this region are essential to uncover the causal variants. Additionally, the limited sample size could potentially impede the ability to detect the association signal. Therefore, in this study, we are investigating the relationship between HNC and HLA loci using an advanced fine-mapping approach and a significantly larger dataset.

In this study, we collect samples from different studies of 19,749 HNC samples from oral cavity, oropharynx, hypopharynx, and larynx subsites, and 38,877 non-HNC control. The raw genotype data was filtered with stringent threshold to obtain only high-quality variants. HLA imputation was performed with Michigan HLA imputation server with recent multi-ethnic HLA imputation panel. Post-imputation QC was applied to obtain high-quality imputed variants. The associations between the variants and HNC were evaluated by adjusting for population structure, imputation batch and gender. Novel HLA loci associated with HNC are expected to be discovered in this study.

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