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headandneck 5000

Investigating the effect of variants at HLA on risk of HPV status in a clinical cohort of people with head and neck cancer

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Scientific Outline

HPV infection is a primary risk factor for oropharyngeal cancer (OPC) and is also known to cause several other cancers (1). Generally, HPV infections are asymptomatic and cleared by the immune system in healthy individuals. However recurrent and persistent infection with any of the 13 oncogenic types of HPV can lead to cancer. Amongst the high-risk HPV types, HPV 16 is the most likely to persist and progress to cancer, although not all cases of oropharyngeal cancer are attributable to this type (2). Furthermore, multiple HPV infections have been found to have a synergistic effect in cervical carcinogenesis (3), which may also be the case for OPC.

Similarly, the combined effects of HPV-16 infection and smoking have been tested in relation to oropharyngeal cancer and classed as independent risk factors by Anantharaman et al (2016) (4).

Due to its association with HPV, sexual behaviour has been identified as a risk factor for OPC. Particularly individuals with a history of multiple oral sex partners are at increased risk for developing OPC (5).

Genetic factors have been implicated in oropharyngeal cancer susceptibility and loci in the human leukocyte antigen (HLA) region were recently identified in a large genome-wide association study (GWAS) of oropharyngeal cancer (6). The HLA region is one of high linkage disequilibrium located on chromosome 6 which plays a pivotal role in immune response. Of note, stratified analysis on a subgroup of OPC cases with controls and information available on HPV status indicated that the association between HLA haplotype and OPC risk was stronger in HPV-positive cancers.

Observed associations in this region are strong and this study encouraged replication of the same HLA susceptibility loci and further scrutiny of their link with HPV.

It is of interest to investigate HLA haplotypes in relation to HPV status and sexual behaviour. We wish to further evaluate the extent and specificity of this HLA effect in HPV-associated cancers. Such evaluation may help elucidate why some individuals are at higher risk of HPV-positive OPC after HPV infection and may also improve understanding of the prognosis of HPV-positive OPC, which is associated with improved therapeutic response and survival than HPV-negative OPC (7).

We propose that specific HLA haplotypes could amplify or reduce the risk of HPV infection among individuals with certain sexual behaviours.

In order to carry out this research access to the "Baseline Data Capture Form" will be necessary as this will provide information regarding the HPV status of participants. The baseline "About You" questionnaire will provide participant demographics and data on alcohol and tobacco use. The "Sexual History" questionnaire can obtain information relating to oral sex, a key risk factor for both HPV and oropharyngeal cancer. Also, medical history for genital conditions may indicate the previous presence of HPV.

The Head and Neck 5000 data will be anonymized during research; it will be provided externally to the HLA*IMP framework for HLA imputation in an anonymized format. Participant information will not be identifiable in the final report.

Summary:

The human leukocyte antigen (HLA) region is one of high linkage disequilibrium located on chromosome 6 which plays a pivotal role in immune response. This study seeks to replicate the findings from a recent Genome Wide Association Study that identified susceptibility loci for oropharyngeal cancer (OPC) in the HLA region. Using HN5000 data we will carry out HLA imputation in this independent population. Two methods of HLA imputation will be compared for accuracy.

A key finding of Lesseur et al's GWAS (2016) that we wish to reproduce and explore further is the protective association afforded by the class II haplotype HLA-DRB1*1301-HLA-DQA1*0103-HLA-DQB1*0603 against HPV-positive oropharyngeal cancer. We propose that HLA haplotypes are associated with HPV status and may show an interaction effect with reported sexual behaviour.

We hope to draw conclusions about the effect of HLA variation on HPV susceptibility. We also hope to identify links between HLA, HPV strain, or any synergistic effects of multiple HPV strains, with

sexual behaviour and cancer susceptibility, including assessment of independent risk factors to assess confounding.

Keywords: Human Leukocyte Antigen (HLA), Human Papilloma Virus (HPV), Sexual Behaviour, Genetic Susceptibility & Quality Control

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