**HLA-A SNPs and amino acid variants are associated with nasopharyngeal carcinoma in Malaysian Chinese**

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**Abbreviations:** λgc: lambda genomic control inflation factor; 3’ UTR: 3’-untranslated region; 5’ UTR: 5’ untranslated region; 95% CI: 95% confidence interval; ASR: age-standardized rate; dbMHC: database for major histocompatibility complex; EA: early antigen; EBV: Epstein–Barr virus; eQTL: expression quantitative trait loci, GWAS: genome wide association study; HKL: Kuala Lumpur General Hospital; HPP: Penang General Hospital; HUS: Hospital University Sarawak; HWE: Hardy–Weinberg equilibrium; IBS: identity-by-state; IgA: immunoglobulin A; ImmPort: Immunology Database and Analysis Portal; LD: linkage disequilibrium; MAF: minor allele frequency; MHC: major histocompatibility complex; NCBI: National Center for Biotechnology Information; NPC: nasopharyngeal carcinoma; OR: odds ratio; PCA: principal component analysis; PROVEAN: Protein Variation Effect Analyzer; Q-Q plot: quantile-quantile plot; QES: Queen Elizabeth Hospital Sabah; r²: Pearson’s correlation coefficient; RIKEN: The Institutes of Physical and Chemical Research; SIFT: Sorting Intolerant from Tolerant; SNP: single nucleotide polymorphism; UMMC: University Malaya Medical Centre; VCA: viral capsid antigen

**Additional Supporting Information may be found in the online version of this article.**


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Nasopharyngeal carcinoma (NPC) arises from the mucosal epithelium of the nasopharynx and is constantly associated with Epstein–Barr virus type 1 (EBV-1) infection. We carried out a genome-wide association study (GWAS) of 575,247 autosomal SNPs in 184 NPC patients and 236 healthy controls of Malaysian Chinese ethnicity. Potential association signals were replicated in a separate cohort of 260 NPC patients and 245 healthy controls. We confirmed the association of HLA-A to NPC with the strongest signal detected in rs3869062 (p = 1.73 × 10⁻⁸). HLA-A fine mapping revealed associations in the amino acid variants as well as its corresponding SNPs in the antigen peptide binding groove (pHLA-A-aa-site-99 = 3.79 × 10⁻⁸, pHLA-A-aa-site-26 = 3.79 × 10⁻⁸) and T-cell receptor binding site (pHLA-A-aa-site-145 = 1.41 × 10⁻⁸, pHLA-A-aa-site-145 = 1.41 × 10⁻⁸) of the HLA-A. We also detected strong association signals in the 5' UTR region with predicted active promoter states (pHLA-A-5UTR = 7.91 × 10⁻³). SNP rs41545520 is a potential binding site for repressor ATF3, with increased binding affinity for rs41545520-G correlated with reduced HLA-A expression. Multivariate logistic regression diminished the effects of HLA-A amino acid variants and SNPs, indicating a correlation with the effects of HLA-A*11:01, and to a lesser extent HLA-A*02:07. We report the strong genetic influence of HLA-A on NPC susceptibility in the Malaysian Chinese.

What’s new?
Certain variants of the HLA-A gene are linked to either resistance or susceptibility in nasopharyngeal carcinoma (NPC). But which variants are most strongly associated with effects in NPC remains unclear. Here, high resolution fine-mapping of the HLA-A region was used to better understand the effects of variants on peptide loading or HLA-A expression in a Malaysian Chinese population. Variants showing potential epigenetic, peptide-loading function and T-cell immune response were correlated with the effects of HLA-A*11:01, a protective HLA-A allele. Most other HLA-A variants did not appear to possess any potential function.