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## The Principal Genetic Determinants for Nasopharyngeal Carcinoma in China Involve HLA Class I Antigen Recognition Groove

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Nasopharyngeal carcinoma is a devastating epithelial malignancy facilitated by Epstein Barr Virus infection that claims over 50,000 lives each year, mostly in East Asia. Here we resolve the major genetic influences for NPC incidence using a genome wide association study (GWAS), independent cohort replication, and full molecular HLA Class I gene typing including 4055 study participants from the Guangxi Zhuang Autonomous Region and Guangdong province of southern China. We detect and replicate strong association signals involving of 58 SNPs across the major histocompatibility complex-HLA-A,-B and -C Class I genes ( $P_{\text{combined}}=7.4 \times 10^{-29}$ ;  $P_{\text{combined}}=6.5 \times 10^{-19}$ ;  $P_{\text{combined}}=6.8 \times 10^{-8}$  respectively). Approximately 300 SNP and amino acid variants driven by linkage disequilibrium within HLA were analyzed in concert to resolve separate and largely independent HLA-A, -B and -C gene influences. The exercise collapsed replicated associations in adjacent genes (HLA-A, OR2H1, GABBR1, HCG9 and HLA-F) as proxies

for the HLA- A\*11:01 resistance phenotype and implicates specific Class I peptide recognition motifs in HLA-A and B peptide binding groove. Along with HLA we replicate four additional NPC associated loci, TNFRSF19 (CHR 13), MDS1-EV11(CHR 3;) and CDNK2A/2B ( CHR 9) and TMEM179 (CHR 14), to affirm the principal genetic influences on NPC onset in China.