Table S1. Number of selected immune genes in each sub-pathway

Sub-pathway annotation	No. of genes
Release of cancer cell antigens	74
Cancer antigen presentation	101
T-cell priming and activation	150
Immune cell localization to tumors	292
Stromal Factors	102
Recognition of cancer cells by T-cells	111
Killing of cancer cells	179
Myeloid cell activity	260
NK cell activity	28
Cell cycle and proliferation	54
Tumor-intrinsic factors	155
Immunometabolism	101
Common signaling pathways: Wnt, TGF-β, NF-kB, TLR, and Jak/STAT	162
Total Immune Genes	**757**
Known GWAS genes from prior HNSCC	115
Human leukocyte antigen region (6p21.2)	44
Killer cell immunoglobulin-like receptors cluster	17
Innate Database	950
Total combining genes	**1576**

Abbreviation: GWAS, genome-wide association studies; HNSCC, head and neck squamous cell carcinoma; OPC, oropharyngeal cancers.

Table S2. Functional enrichment analyses of the top-ranked susceptibility genes using Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and Gene Ontology (GO)

Pathway	Candidate genes presented	Background gene count	*P*-value
Overall HNSCC susceptibility genes			
Immunoglobulin complex	*ICAM5*, *HLA-DRB1*, *HLA-DQA1*	3 of 43	0.002
Regulation of leukocyte differentiation	*FANCA*, *HLA-DRB1*	2 of 261	0.047
Non-OPC susceptibility genes			
Cellular response to stress	*TP73*, *FANCA*, *IRAK2*, *TPM1*, *MGMT*	5 of 139	0.014
Neurotrophin signaling pathway	*TP73*, *IRAK2*	2 of 116	0.016
OPC/HPV-positive OPC susceptibility genes			
MHC class II protein complex	*HLA-DRB1, HLA-DRB5, HLA-DQA1, HLA-DRA, HLA-DMB, HLA-DQB2*	6 of 14	2.9×10^{-15}
Common signaling	*CDH2, CDH5, NTN1, LOXL2, HLA-DRB1, HLA-DRB5, HLA-DQA1, HLA-DRA, HLA-DMB, HLA-DQB2*	10 of 162	1.3×10^{-12}
Autoimmune thyroid disease	*HLA-DRA, HLA-DRB1, HLA-DRB5, HLA-DQA1, HLA-DMB*	5 of 49	4.4×10^{-8}
Risk factor sub-group susceptibility genes for Overall HNSCC (smoking, alcohol, overweight/obese)			
Viral myocarditis	*CAPS8, HLA-DPB2, HLA-G, HLA-DOA*	4 of 56	3.4×10^{-7}
Regulation of T cell activation	*NFkB-p65, FANCA, CD6, CD68, CD74/HLA-DG, SOCS6, HLA-G, HLA-DOA, HLA-DPB2*	9 of 302	2.8×10^{-6}
Cell adhesion molecules	*CD6, CDH2, CDH5*, *HLA-G*, *HLA-DOA, HLA-DPB2*	6 of 139	7.8×10^{-4}

Abbreviation: HNSCC, head and neck squamous cell carcinoma; OPC, oropharyngeal cancers; HPV, human papillomavirus.

Table S3. The high-confident pair-wise protein-protein interaction (PPI) score, predicted by STRING (Search Tool for the Retrieval of Interacting Genes)

Interaction pairs		**Evidence**		**Combined PPI score**
Protein (node 1)	**Protein** (node 2)	Experimentally	Database	
CDH2	CDH5	0	0.9	0.92
IRAK2	NFkB-p65	0	0.9	0.93
CASP8	NFkB-p65	0	0.9	0.95
cKIT	SOCS6	0.47	0.9	0.97
CD74/HLA-DG	HLA-DOA	0.19	0.9	0.95
CD74/HLA-DG	HLA-DMB	0.38	0.9	0.99
CD74/HLA-DG	HLA-DRB5	0.35	0.9	0.99
CD74/HLA-DG	HLA-DQA1	0.70	0.9	0.99
CD74/HLA-DG	HLA-DQB2	0.41	0.9	0.99
CD74/HLA-DG	HLA-DRB1	0.86	0.9	0.99
CD74/HLA-DG	HLA-DRA	0.89	0.9	0.99
HLA-DMB	HLA-DOA	0.48	0.9	0.97
HLA-DMB	HLA-DQA1	0.27	0.9	0.96
HLA-DMB	HLA-DRB1	0.39	0.9	0.98
HLA-DMB	HLA-DRA	0.76	0.9	0.99
HLA-DOA	HLA-DRB5	0.20	0.9	0.93
HLA-DOA	HLA-DQB2	0.20	0.9	0.94
HLA-DOA	HLA-DRB1	0.20	0.9	0.94
HLA-DQA1	NCAM1/CD56	0	0.9	0.91
HLA-DQA1	HLA-DRB5	0.35	0.9	0.96
HLA-DQA1	HLA-DRB1	0.35	0.9	0.96
HLA-DQA1	HLA-DQB2	0.74	0.9	0.99
HLA-DQB2	HLA-DRA	0.30	0.9	0.95
HLA-DRA	HLA-DRB1	0.93	0.9	0.99
HLA-DRA	HLA-DRB5	0.93	0.9	0.99
HLA-DRB1	NCAM1/CD56	0	0.9	0.92
HLA-DRB1	HLA-DRB5	0.75	0.9	0.98
HLA-G	NCAM1/CD56	0	0.9	0.95