Table S1. Patients and samples included in dataset, Related to Figure 1.

Designation	Age/Sex	Primary Site	Lymph Node(s) Collected	Pathologic Stage	Grade	PNI	LVI	ECE
MEEI5	69/F	Left lateral tongue	Left level 2	T2N1	2	Present	Present	Absent
MEEI6	88/F	Right floor of mouth	Left level 2	T4aN2c	1	Present	Present	Present
MEEI7	71/F	Right floor of mouth	--	T1N2b	3	Absent	Present	Present
MEEI8	82/F	Right hard palate	--	T4aN0	1	Absent	Absent	--
MEEI9	77/F	Right lateral tongue	--	T1N0	2	Absent	Absent	--
MEEI10	76/M	Right retromolar trigone	--	T4aN2b	2	Absent	Absent	Present
MEEI12	80/M	Left retromolar trigone	--	T4aN0	2	Present	Present	--
MEEI13	52/F	Left lateral tongue	--	T3N1	2	Present	Present	Absent
MEEI16	63/F	Left lateral tongue	--	T2N0	1	Absent	Absent	--
MEEI17	59/M	Right alveolar ridge	--	T4aN0	2	Present	Absent	--
MEEI18	41/M	Left lateral tongue	--	T3N1	2	Present	Present	Absent
MEEI20	53/M	Right floor of mouth	Right level 3	T4aN2c	2	Present	Present	Present
MEEI22	77/M	Left buccal mucosa	--	T1N0	2	Absent	Absent	--
MEEI23	56/M	Right retromolar trigone	--	T3N1	2	Absent	Present	Absent
MEEI24	78/F	Right alveolar ridge	--	T4aN2c	2	Absent	Absent	Absent
MEEI25	76/F	Left lateral tongue	Left level 2	T3N1	2	Present	Present	Present
MEEI26	51/M	Left floor of mouth	Right and left level 1	T4aN2c	3	Present	Present	Absent
MEEI28	58/M	Right lateral tongue	Left level 2	T2N2c	1	Present	Present	Absent

PNI = perineural invasion; LVI = lymphovascular invasion; ECE = extracapsular extension

Table S2. Clinical and pathologic features of deeply sequenced samples, Related to Figure 1. p16 immunohistochemistry and HPV *in situ* hybridization were negative for all samples.

Designation	Primary Site	Size (cm)	Description	LN Involved	Stage	Grade	PNI	LVI	ECE	p16 IHC	HPV PCR
MEEI 5	L lateral tongue	3.8	Invasive SCC, keratinizing	1/21, L level 2, < 1.0cm	T2N1	2	Present	Present	Absent	(-)	(-)
MEEI 6	R floor of mouth	3.9	Invasive SCC, keratinizing, involving bone	5/34, bilateral, largest 1.8cm	T4aN2c	1	Present	Present	Present	(-)	(-)
MEEI 16	L lateral tongue	2.2	Invasive SCC, keratinizing	0/23	T2N0	1	Absent	Absent	--	(-)	(-)
MEEI 17	R alveolar ridge	3.8	Invasive SCC, keratinizing, involving bone	0/30	T4aN0	2	Present	Absent	--	(-)	(-)
MEEI 18	L lateral tongue	5.5	Invasive SCC, keratinizing	1/23, L level I, 0.4cm	T3N1	2	Present	Present	Absent	(-)	(-)
MEEI 20	R floor of mouth	5.2	Invasive SCC, non-keratinizing, basaloid, necrotic	5/50, bilateral, largest 3.0cm	T4aN2c	2	Present	Present	Present	(-)	(-)
MEEI 22	L buccal mucosa	2.0	Invasive SCC, keratinizing	Not examined	T1N0	2	Absent	Absent	--	(-)	(-)
MEEI 25	L floor of mouth	6.2	Invasive SCC, keratinzing	1/9, L level 2, 2.5cm	T3N1	2	Present	Present	Present	(-)	(-)
MEEI 26	L floor of mouth	3.6	Invasive SCC, involving bone and muscle	2/72, bilateral, largest 1.6cm	T4aN2c	3	Present	Present	Absent	(-)	(-)
MEEI 28	R lateral tongue	3.0	Invasive SCC, keratinzing	4/20, bilateral, largest 2.1cm	T2N2c	1	Present	Present	Absent	(-)	(-)

L = left; R = right; SCC = squamous cell carcinoma; PNI = perineural invasion; LVI = lymphovascular invasion; ECE = extracapsular extension; IHC = immunohistochemistry; HPV = human papillomavirus; PCR = polymerase chain reaction

Table S3. Mutations and copy number variations detected in profiled primary tumors, Related to Figure 1. Common mutations evaluated by whole exome sequencing of a subset of samples and SNaPshot next generation sequencing assay of all samples include the top 5 mutations in TCGA HNSCC tumors, as well as mutations in TERT promoter. CNVs evaluated include top 4 abnormalities noted in TCGA HNSCC tumors.

		Reported	MEEI5	MEEI6	MEEI16	MEEI17	MEEI18	MEEI20	MEEI22	MEEI25	MEEI26	MEEI28
Common Mutations	TP53	72%[a]	**Mut[1,2]**	**Mut[2]**	ND	ND	**Mut[2]**	**Mut[1,2]**	**Mut[2]**	**Mut[1,2]**	**Mut[1,2]**	ND
	TERT promoter	30%[b]	**Mut[2]**	ND	**Mut[2]**	**Mut[2]**	ND	ND	**Mut[2]**	**Mut[2]**	ND	**Mut[2]**
	FAT1	23%[a]	ND	ND	ND	ND	ND	ND	ND	**Mut[1]**	ND	ND
	CDKN2A	22%[a]	ND	ND	ND	ND	ND	**Mut[1,2]**	**Mut[2]**	**Mut[1]**	ND	ND
	PIK3CA	21%[a]	**Mut[1,2]**	ND	ND	ND	**Mut[2]**	ND	ND	ND	ND	ND
	NOTCH1	19%[a]	ND	ND	ND	ND	ND	**Mut[1]**	ND	ND	ND	**Mut[1]**
Other	--	--	**TSC2[2]**	**FBXW7[2]**	--	**AJUBA[1], FBXW7[2]**	**MET[2], BRCA2[2]**	**NSD1[1]**	--	--	**NFE2L2[1]**	**AJUBA[1], TGFBR2[1], SMARCB1[2], CIC[2]**
CNVs	3p loss	57%	**++**	**+**	ND	ND	**++**	**++**	**++**	ND	ND	ND
	3q gain	44%	**++**	**+**	**++**	ND	**++**	**++**	**++**	ND	**++**	ND
	8p loss	29%	**++**	ND	ND	ND	**++**	**+**	**+**	**++**	ND	**+**
	8q gain	56%	**++**	**+**	ND	ND	**++**	**++**	**++**	**++**	ND	ND

[a] Reported in TCGA; [b] reported in Morris et al. (2016); Mut = mutation detected; ND = mutation not detected; [1] mutation detected by whole exome sequencing; [2] mutation detected by SNaPshot; CNV = copy number variation

Table S5. Differentially expressed genes between CAF subsets, Related to Figure 2. Genes are sorted from most to least significant.

CAF1 genes					CAF2 genes				
Genes 1-50	**Genes 51-100**	**Genes 101-150**	**Genes 151-200**	**Genes 201-208**	**Genes 1-50**	**Genes 51-100**	**Genes 101-150**	**Genes 151-200**	**Genes 201-241**
CTHRC1	COL5A2	CPXM1	LOXL3	CXCL6	CFD	ANGPTL1	CLU	FBLN5	TMEM176A
COL1A1	GBP1	RGS3	COL6A2	FBXO32	APOD	JUNB	LHFP	SCARA5	ADH5
POSTN	ITGB1	MYO1B	GEM	FKBP10	CXCL12	RPL13A	NDRG2	PROS1	IL11RA
TPM4	IL24	WBP5	TGFBI	PTS	GPC3	CILP	SOD3	FOXO3	C5orf4
MFAP2	PLAU	MYH9	SGCB	SMIM3	SEPP1	MEG3	TFPI	RECK	CYP27A1
SPARC	AEBP1	ITGB5	PDLIM3	TRIB2	GSN	JUN	NFIB	SLPI	CBLB
WNT5A	COL1A2	SEC23A	FKBP9	HEPH	CXCL14	CD34	MTUS1	RPL22	PID1
COL3A1	TPM2	HSPB1	EDNRA	RRBP1	MFAP4	FOSB	TENC1	ANKRD36BP1	EGFR
LOC541471	CLEC11A	FRMD6	ITM2C		GPX3	MTRNR2L1	EBF1	EBF2	TMEM159
TNFRSF12A	AXL	PDLIM7	CRISPLD2		MGP	VIM	STOM	ECHDC2	MT1M
INHBA	ADAMTS2	PRKCDBP	F2RL2		SPARCL1	CHRDL1	ZFAS1	AGT	PPP1R10
THY1	IGFBP3	ILK	RCN1		LTBP4	SERPINA3	SAMHD1	NPDC1	ARHGAP10
SERPINH1	GREM1	WIPI1	IL8		ADH1B	TIMP3	IGFBP5	DDIT3	NID1
LOXL2	MMP1	CDH11	RAB2A		ZBTB16	TGFBR3	KLF4	TPPP3	SLIT3
RAB31	DUSP14	PLAT	F2R		ABCA8	NTRK2	CDO1	PLSCR4	CRTAP
GPM6B	TAGLN	SGIP1	SEC31A		C3	MYOC	ADAM33	NXF1	CAB39L
ACTN1	PPIC	STEAP1	C12orf75		IGF1	THBS4	PCDHGC3	F10	CDC42EP4
IFI27	REEP3	PON2	STARD13		PODN	CST3	PRNP	AKR1C3	SLC19A2
LGALS1	RAP1B	HAS2	TWSG1		PRELP	PLAC9	EPB41L2	PDGFD	SLC40A1
SERPINE1	TNFRSF21	PTEN	MRPL32		PDK4	PI16	FBLN2	CTSF	SPG20
PLAUR	CTSK	FMOD	RSU1		FHL1	IGFBP6	GADD45B	FCGRT	CALCOCO1
HIF1A	SPON2	CALD1	FBN1		ABI3BP	IER2	VAT1	RARRES1	SDC2
CHN1	RARRES2	MMP3	B4GALT1		RNASE4	FGL2	PLAGL1	MATN2	BCL6
THBS2	LEPRE1	PHLDA2	VCL		PLA2G2A	RPL14	CFH	ZNF460	DDX39B
ASPN	RHOC	P4HA2	TDO2		BTG2	COL14A1	BTF3	CYR61	GPNMB
TNC	PRSS23	ECM1	CCL2		TNXB	RAMP2	KIAA1683	CDKN1A	MT1A
ARF4	H1F0	SNAI2	MARCKS		CYBRD1	DHRS3	ESD	INMT	BDH2
CALU	PLOD2	FNDC3B	CNIH4		FBLN1	OLFML3	EDNRB	EIF1B	ENPP2
LUM	KIAA1217	UBD	GOLM1		HSPB6	ABLIM1	MYC	SOCS3	SYNPO2
TWIST1	C1QTNF6	BMP1	CNN3		MGST1	CD302	LEPR	APP	IL6ST
MMP11	CPE	SDC4	STEAP2		ZFP36	CCDC80	GAS6	ITIH5	SERINC1
SPHK1	IFITM1	FAP	DKK3		VIT	RBMS3	DDAH2	GABARAPL1	TRIP10
PRDM1	MYL6	NPTN	ANXA5		SFRP1	MT1X	FIBIN	GSTM2	PLBD1
NREP	PHLDA1	GNAI1	TMEM30A		ADAMTS1	FOS	C7	RASD1	PHF17
LY6E	LTBP1	CLIC4	MRPS24		MAMDC2	CAPN6	SPTBN1	NR4A1	MT1E
TNFAIP6	ANTXR1	AQP1	MMP19		PLTP	LAMA2	RPL10A	NT5E	NFKBIZ
BPGM	YIF1A	ITGA1	EPAS1		SRPX	HSPA1B	ITM2B	MAP1LC3C	MOB3B
COL5A1	CRABP2	LAMP5	KCTD10		PDGFRL	ABCA6	BRD2	EPB41L4A-AS1	SELENBP1
CAV1	ITGA5	FADS1	IER3IP1		ALDH1A1	MFAP5	CPQ	ACVR2A	TCEA3
TMEM45A	COL6A3	MYL9	TNFRSF6B		EFEMP1	FXYD6	HSD17B11	RPS4Y1	AKAP12
COL12A1	TWIST2	SELM	CD59		A2M	OGN	CEBPD	TNFAIP2	PPAP2A
PXDN	SULF1	FN1	ID1		MTRNR2L2	LRP1	GSTM5	FAM13C	
PDPN	C1orf198	ANGPTL2	DDAH1		SMOC2	PPP1R15A	SESN1	CPED1	
RIN2	SRPX2	HAPLN3	STC1		MTRNR2L8	COL15A1	PDGFRA	TGFBR2	
S100A16	LMCD1	SULF2	SLC39A6		PTGDS	ADIRF	ANG	SCPEP1	
IL1R1	KDELR3	FAM114A1	PGM3		NFIA	ALDH2	FMO2	RND3	
PTK7	PKIG	ID3	PLOD1		DPT	PPAP2B	CTGF	HSPB8	
TPM1	IFIT3	TSKU	C12orf23		FGF7	METTL7A	BMP4	SGCE	
RCN3	VMP1	ACTA2	CTTN		ITM2A	WISP2	ZFAND5	ASS1	
COL6A1	RABAC1	C5orf15	GGT5		FIGF	LGALS3	GALNT16	LAMB2	

Table S7. Six meta-signatures, each derived from multiple related NNMF programs, Related to Figure 3. Genes in each program are ordered from most to least significant.

Cell Cycle		p-EMT		Epi dif. 1		Epi dif. 2		Stress		Hypoxia	
Genes 1-50	**Genes 51-100**	**Genes 1-50**	**Genes 51-100**	**Genes 1-50**	**Genes 51-100**	**Genes 1-50**	**Genes 51-100**	**Genes 1-50**	**Genes 51-100**	**Genes 1-50**	**Genes 51-100**
TK1	MCM5	SERPINE1	ARPC1B	IL1RN	MALAT1	LY6D	UBE2L6	FOS	C1R	NDRG1	ZFP36L1
HMGB2	PLK1	TGFBI	APP	SLPI	TRIP10	KRT16	WDR74	ATF3	PHLDA2	IGFBP3	HLA-E
ZWINT	GGH	MMP10	MFAP2	CLDN4	CAST	KRT6B	PPIF	NR4A1	DNAJB14	PTHLH	PIK3IP1
MAD2L1	MCM4	LAMC2	MPZL1	S100A9	TMPRSS4	LYPD3	PRMT5	DUSP1	MCL1	EGLN3	CLK3
TUBA1B	CENPN	P4HA2	DFNA5	SPRR1B	TOM1	KRT6C	VSNL1	ZFP36	HERPUD1	BNIP3	POLR1D
STMN1	TMPO	PDPN	MT2A	PVRL4	A2ML1	TYMP	VPS25	PPP1R15A	ADRB2	NDUFA4L2	BTG1
KIF22	CDCA3	ITGA5	MAGED2	RHCG	MBOAT2	FABP5	SNRNP40	SGK1	EIF4A3	ERO1L	NPC2
CKS1B	DEK	LAMA3	ITGA6	SDCBP2	LGALS3	SCO2	ADRM1	EGR1	TACSTD2	P4HA1	LAMP2
H2AFZ	RPA2	CDH13	FSTL1	S100A8	ERO1L	FGFBP1	NDUFS8	ZC3H12A	ID1	SLC2A1	DSG2
CENPW	KIF2C	TNC	TNFRSF12A	APOBEC3A	EHF	JUP	TUBA1C	JUNB	ETS2	ENO2	SAT1
CDC20	CDK1	MMP2	IL32	GRHL1	LCN2	IMP4	TMEM79	FOSB	CD74	HK2	AK4
DTYMK	CDCA5	EMP3	COPB2	SULT2B1	YPEL5	DSC2	UQCRFS1	IER2	TRIB1	PGF	SMS
UBE2C	LSM4	INHBA	PTK7	ELF3	ALDH3B2	TMBIM1	EIF3K	NFKBIA	SLC20A1	LDHA	FRMD6
UBE2T	KNSTRN	LAMB3	OCIAD2	KRT16	DMKN	KRT14	NME2	NFKBIZ	LOC284454	PGK1	CLDND1
NUSAP1	TUBG1	VIM	TAX1BP3	PRSS8	PIK3IP1	C1QBP	PKP3	HBEGF	EIF1	PDK1	ACP5
RRM2	SMC4	SEMA3C	SEC13	MXD1	CEACAM6	SFN	SERPINB1	BTG2	CXCL2	DHRS3	AP1G2
BIRC5	CSE1L	PRKCDBP	SERPINH1	S100A7	OVOL1	S100A14	RPL26L1	SOD2	BRD2	DDIT4	TPI1
RNASEH2A	UHRF1	ANXA5	TPM4	KRT6B	TMPRSS11E	RAB38	EIF6	CDKN1A	RASD1	PVRL4	PLAUR
PCNA	RANBP1	DHRS7	MYH9	LYPD3	CD55	GJB5	DSP	NCOA7	LDLR	GPNMB	BCL10
TUBB	CDCA8	ITGB1	ANXA8L1	TACSTD2	KLK6	MRPL14	PHLDA2	JUN	EGR2	BIK	TMEM59
KPNA2	MCM2	ACTN1	PLOD2	CDKN1A	SPRR2D	TRIM29	S100A16	MYC	TFRC	GJB6	HAS3
ASF1B	RFC2	CXCR7	GALNT2	KLK11	NDRG2	ANXA8L2	LGALS7	SERTAD1	ADM	C4orf3	SERINC1
TRIP13	HMGN2	ITGB6	LEPREL1	GPRC5A	CD24	KRT6A	MT1X	CCNL1	TGIF1	IGFBP2	C1orf43
CCNB1	ATAD2	IGFBP7	MAGED1	KLK10	HIST1H1C	PDHB	UQCRC2	RND3	HLA-DRB1	FAM162A	ENO1
TPX2	HAT1	THBS1	SLC38A5	TMBIM1	LY6D	AKR1B10	EIF3I	PLK2	OSR2	GPI	CSDA
CCNB2	PKMYT1	PTHLH	FSTL3	PLAUR	CLIP1	LAD1	MRPL24	SOCS3	SAA1	LPIN3	PFKP
TYMS	SIVA1	TNFRSF6B	CD99	CLDN7	HIST1H2AC	DSG3	CCT7	DNAJB1	ELF3	PLAU	KLHL24
PTTG1	FANCI	PDLIM7	F3	DUOXA1	BNIPL	MRPL21	RHOV	DUSP2	CLK1	ADM	HIST1H1C
KIAA0101	ECT2	CAV1	PSAP	PDZK1IP1	QSOX1	NDUFS7	ECE2	TSC22D1	PER2	ANGPTL4	RBPJ
GMNN	POLE3	DKK3	NMRK1	NCCRP1	ECM1	PSMD6	SSBP1	KLF10	KLF4	DARS	BHLHE40
DNAJC9	WDR34	COL17A1	FKBP9	IDS	DHRS3	AHCY	POLDIP2	GADD45B	GPNMB	NUPR1	GAPDH
CCNA2	MCM3	LTBP1	DSG2	PPL	PPP1R15A	GBP2	FIS1	PMAIP1	MXD1	SERPINE1	UPK3BL
CKS2	NCAPG2	COL5A2	ECM1	ZNF750	TRIM16	TXN2	CKMT1A	MAFF	UBC	PGAM1	LTBP1
MLF1IP	TUBB6	COL1A1	HTRA1	EMP1	AQP3	PSMD13	GJB3	ERRFI1	HLA-DRA	ALDOA	P4HA2
VRK1	NCAPD2	FHL2	SERINC1	CLDN1	IRF6	NOP16	NME1	SLC38A2	SLC3A2	DAAM1	HBP1
CENPM	GINS2	TIMP3	CALU	CRB3	CSTA	EIF4EBP1	MRPS12	IRF1	OVOL1	CXADR	GRHL1
PRC1	TIMELESS	PLAU	TPST1	CYB5R1	RAB25	MRPL12	GPS1	TOB1	HIST1H2BK	SEMA4B	DDIT3
SPAG5	RAD51	LGALS1	PLOD3	DSC2	HOPX	HSD17B10	ALG3	ID2	DDX3X	CA9	ANXA1
TOP2A	CMC2	PSMD2	IGFBP3	S100P	GIPC1	LGALS7B	MRPL20	KLF6	LAMB3	CIB1	ITGA5
AURKB	OIP5	CD63	FRMD6	GRHL3	RAB11FIP1	THBD	EMC6	DNAJA1	ZNF622	SPRR1B	LOC100862671
FEN1	TUBB4B	HERPUD1	CXCL14	SPINT1	CSTB	EXOSC4	SRD5A1	TNFAIP3	TUBB2A	PLIN2	PLS3
TMEM106C	APOBEC3B	TPM1	SERPINE2	SDR16C5	KRT6C	APRT	PA2G4	BHLHE40	ZFAND5	WSB1	TSC22D2
RRM1	ORC6	SLC39A14	RABAC1	SPRR1A	PKP1	ANXA8L1	ECSIT	NXF1	IRF6	HILPDA	GLTP
RFC4	C19orf48	C1S	TMED9	WBP2	JUP	ATP5G1	MRPL23	FOSL1	TNF	NOL3	PLOD2
MCM7	SNRNP25	MMP1	NAGK	GRB7	MAFF	S100A2	NAA20	IER3	BTG1	PFKFB3	PERP
CDKN3	RFC3	EXT2	BMP1	KLK7	DSG3	TBRG4	HMOX2	DUSP6	LMNA	IFNGR1	MALL
NUDT1	TROAP	COL4A2	ESYT1	TMEM79	AKTIP	MAL2	COA4	HCAR2	MAP1LC3B	H1F0	CTNND1
PBK	EBP	PRSS23	STON2	SBSN	KLF3	NHP2L1	DCXR	IL8	TSC22D3	KDM3A	KDM5B
MELK	DKC1	SLC7A8	TAGLN	PIM1	HSPB8	DDX39A	PSMD8	CYR61	PLK3	BCL6	AHNAK2
ANLN	H2AFV	SLC31A2	GJA1	CLIC3	H1F0	ZNF750	WBSCR22	EFNA1	KLHL21	BNIP3L	PNRC1