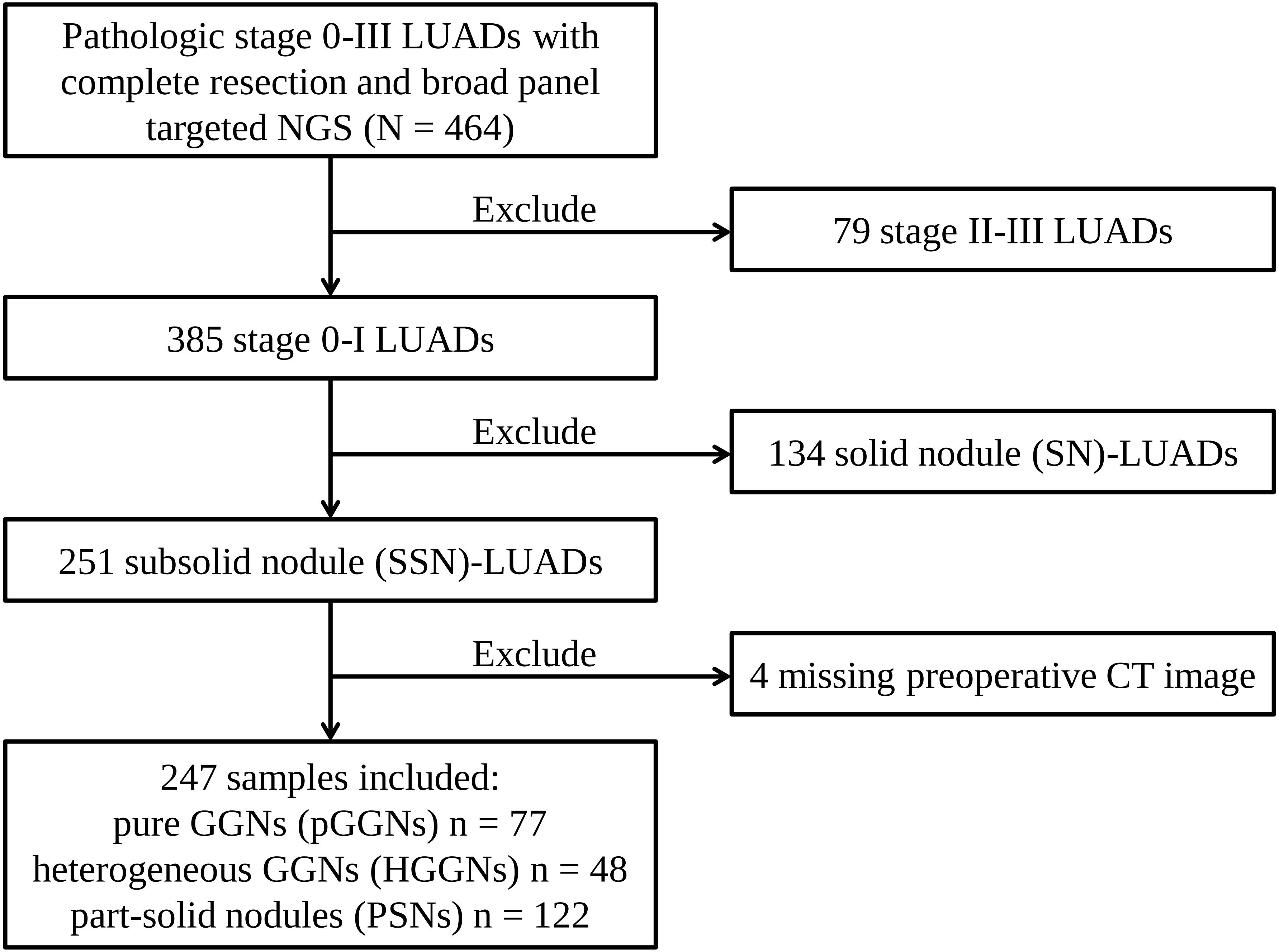
Supplementary Figure 1



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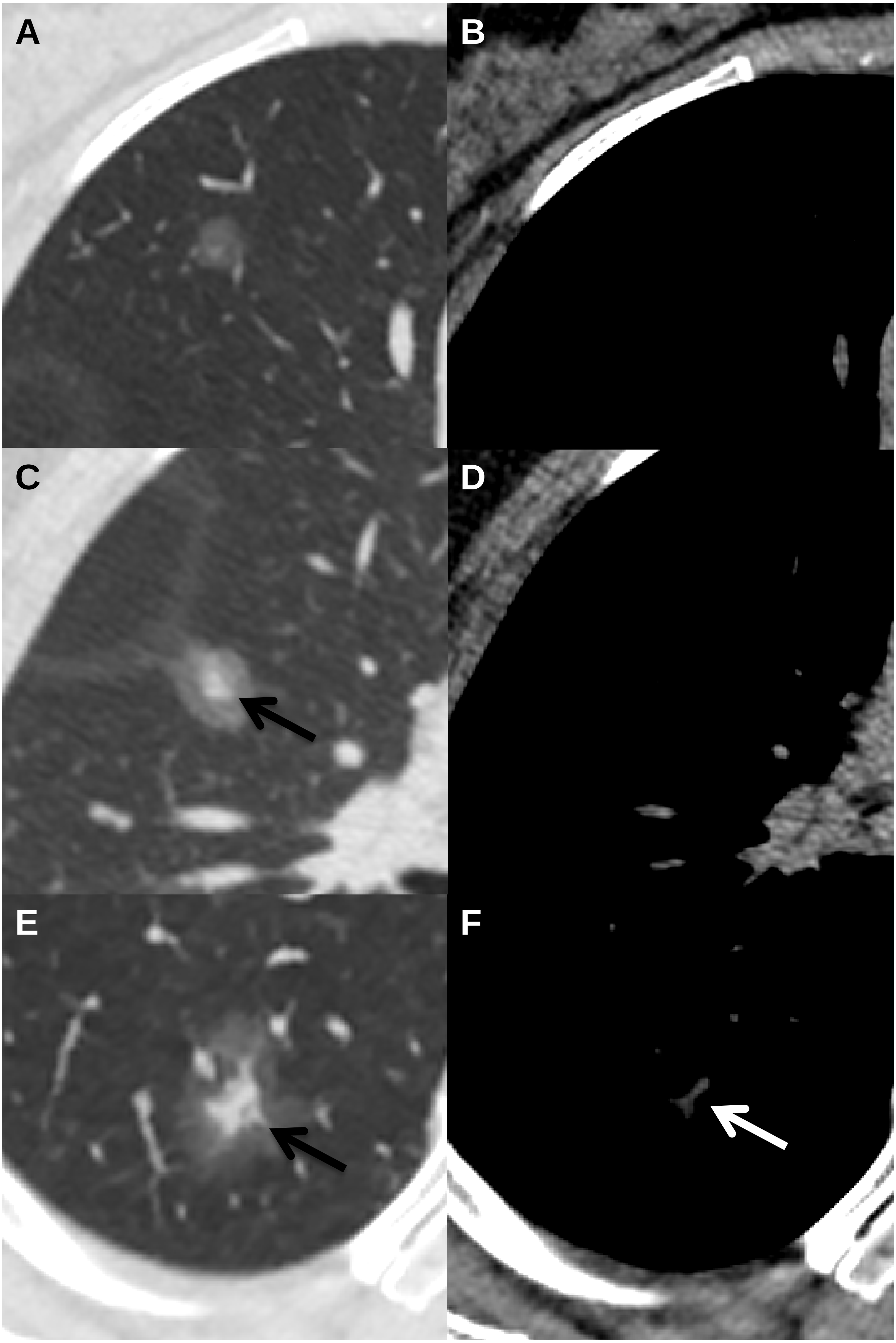
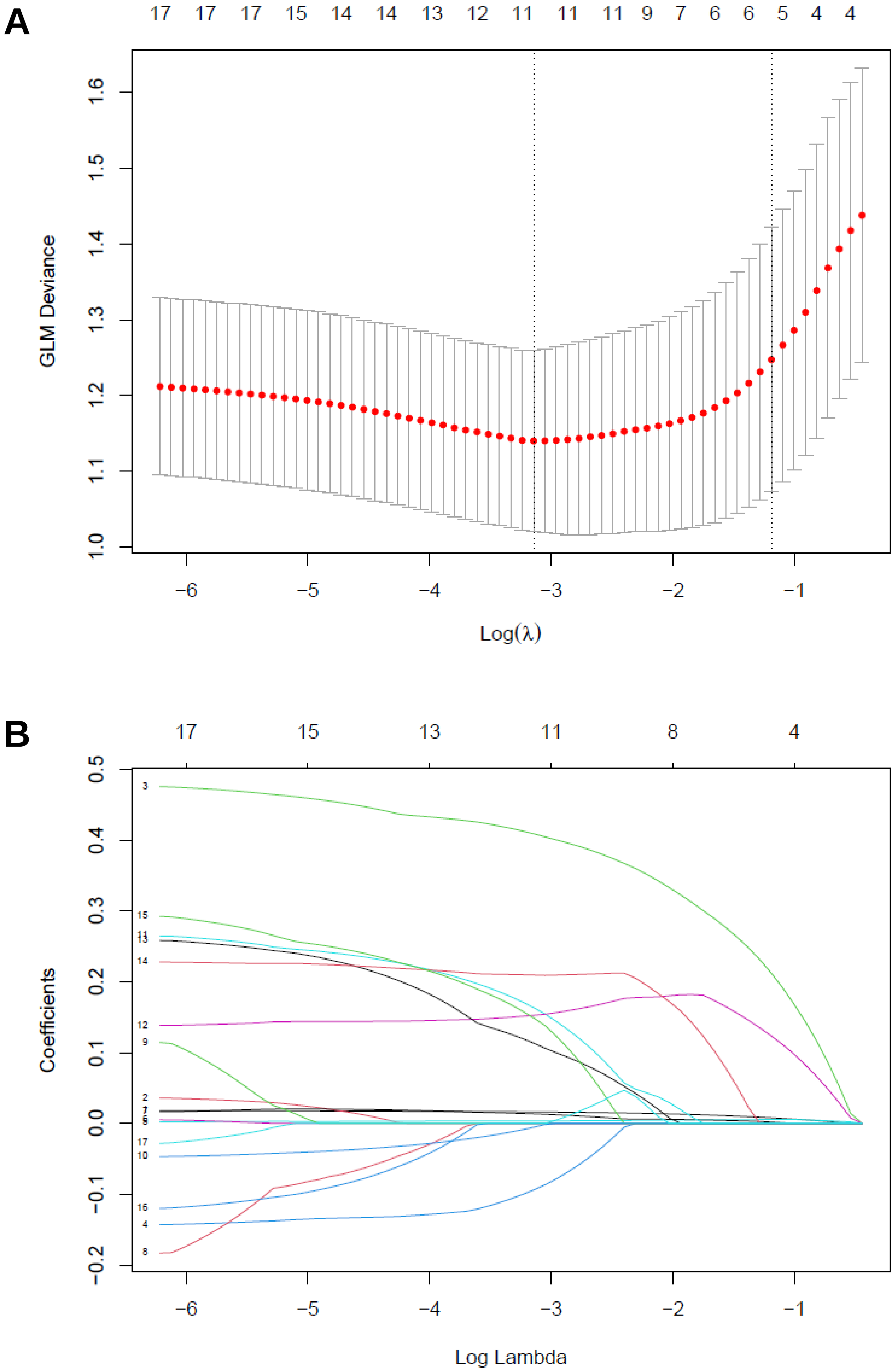


Supplementary Figure 3



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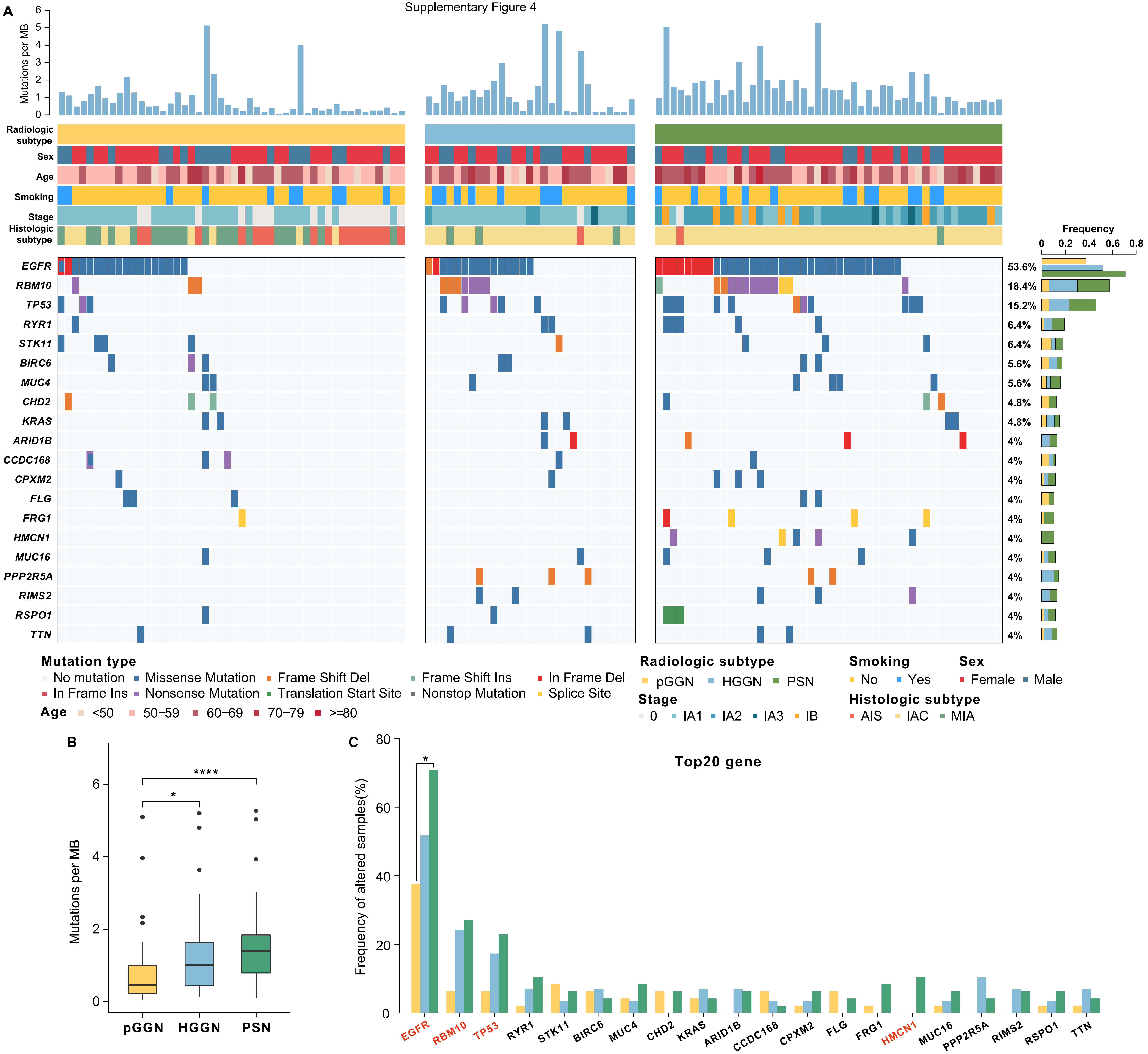

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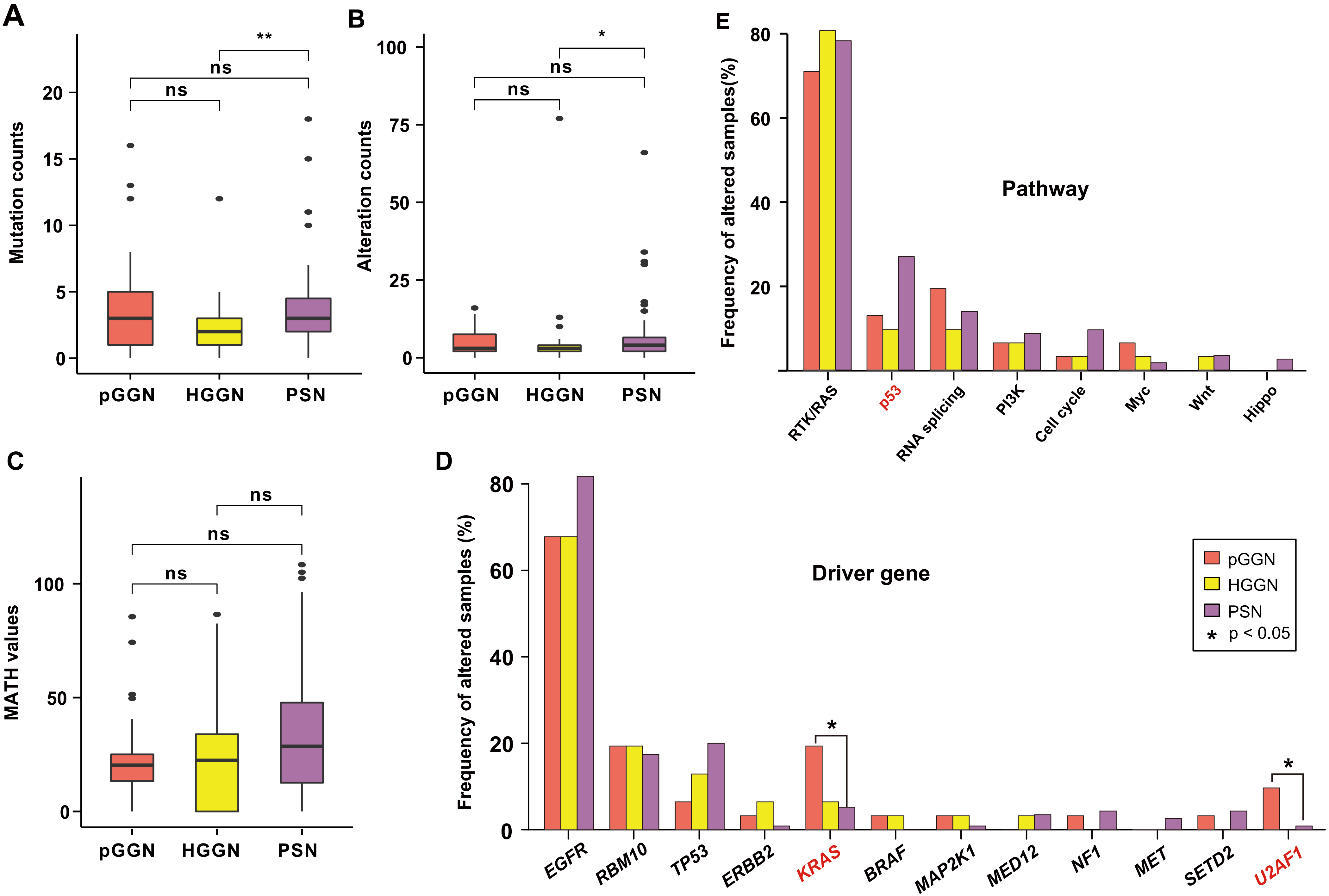

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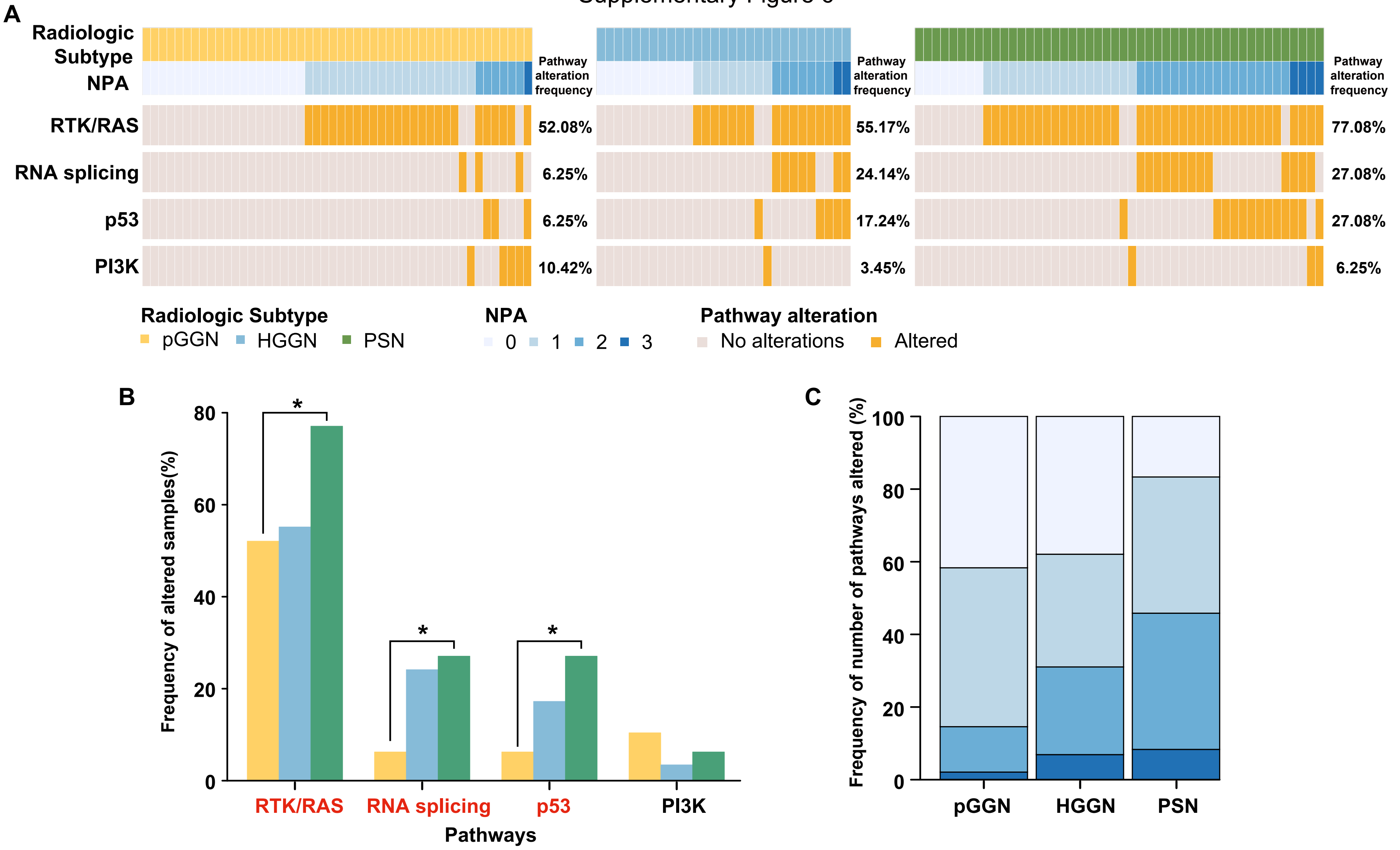
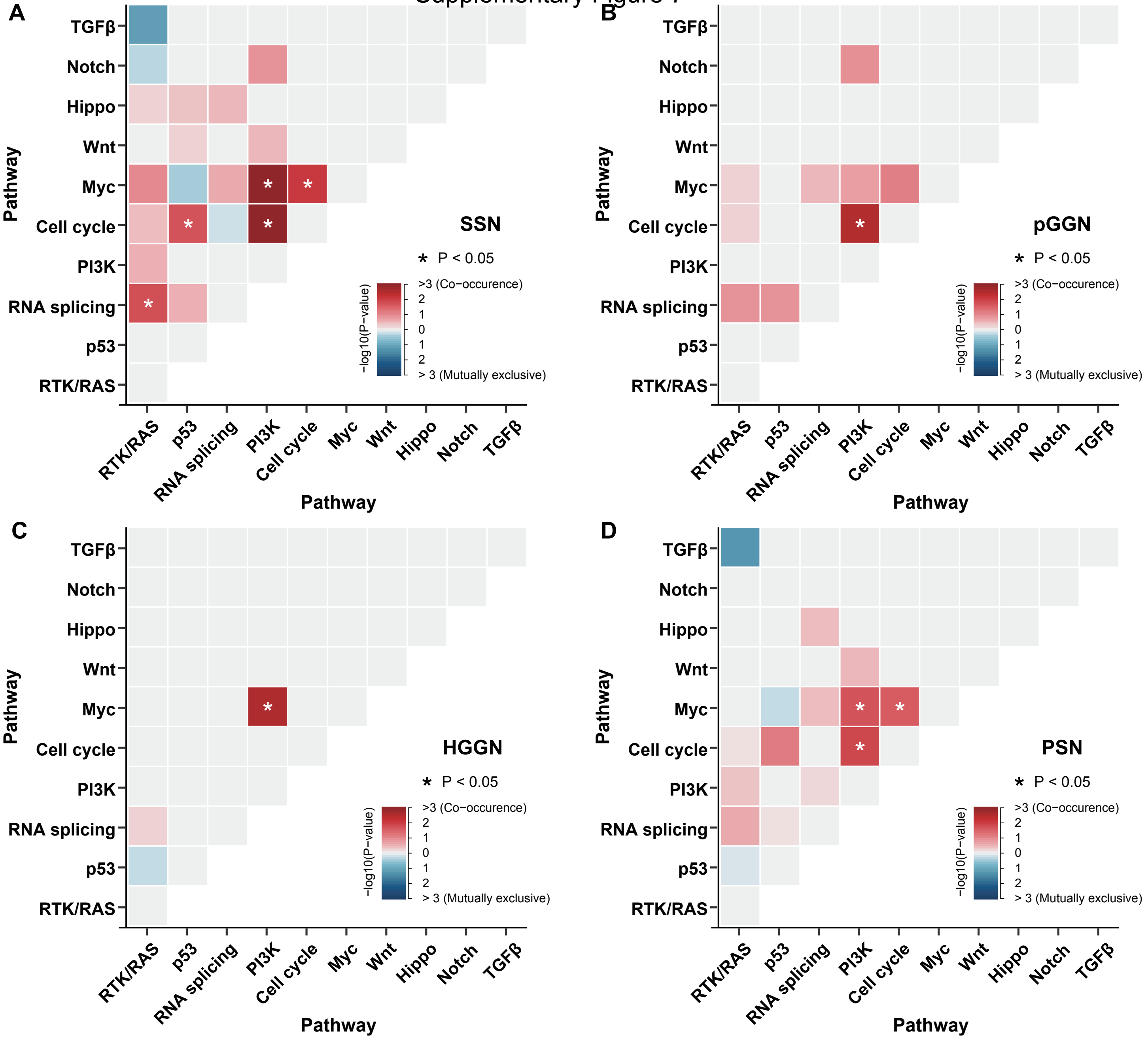
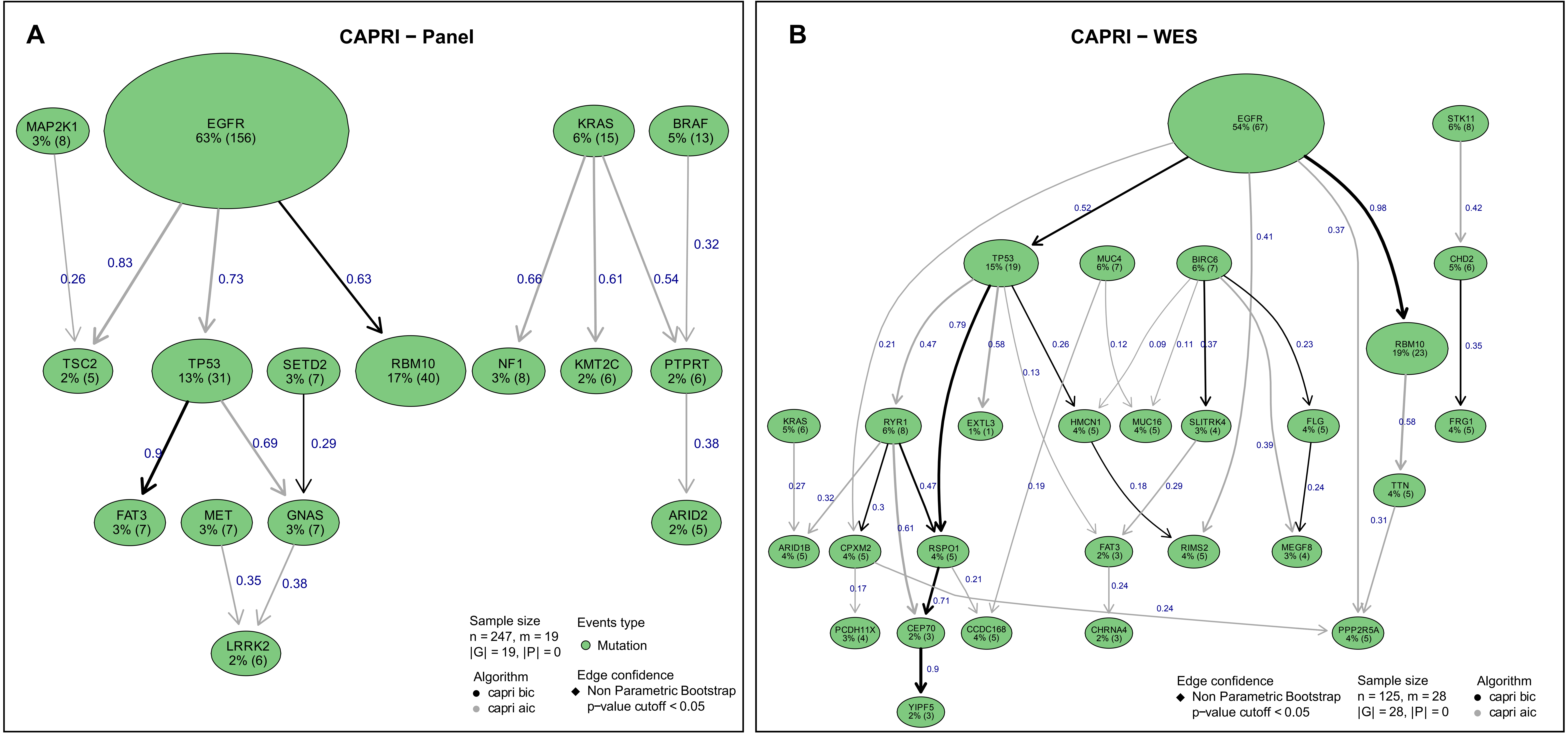


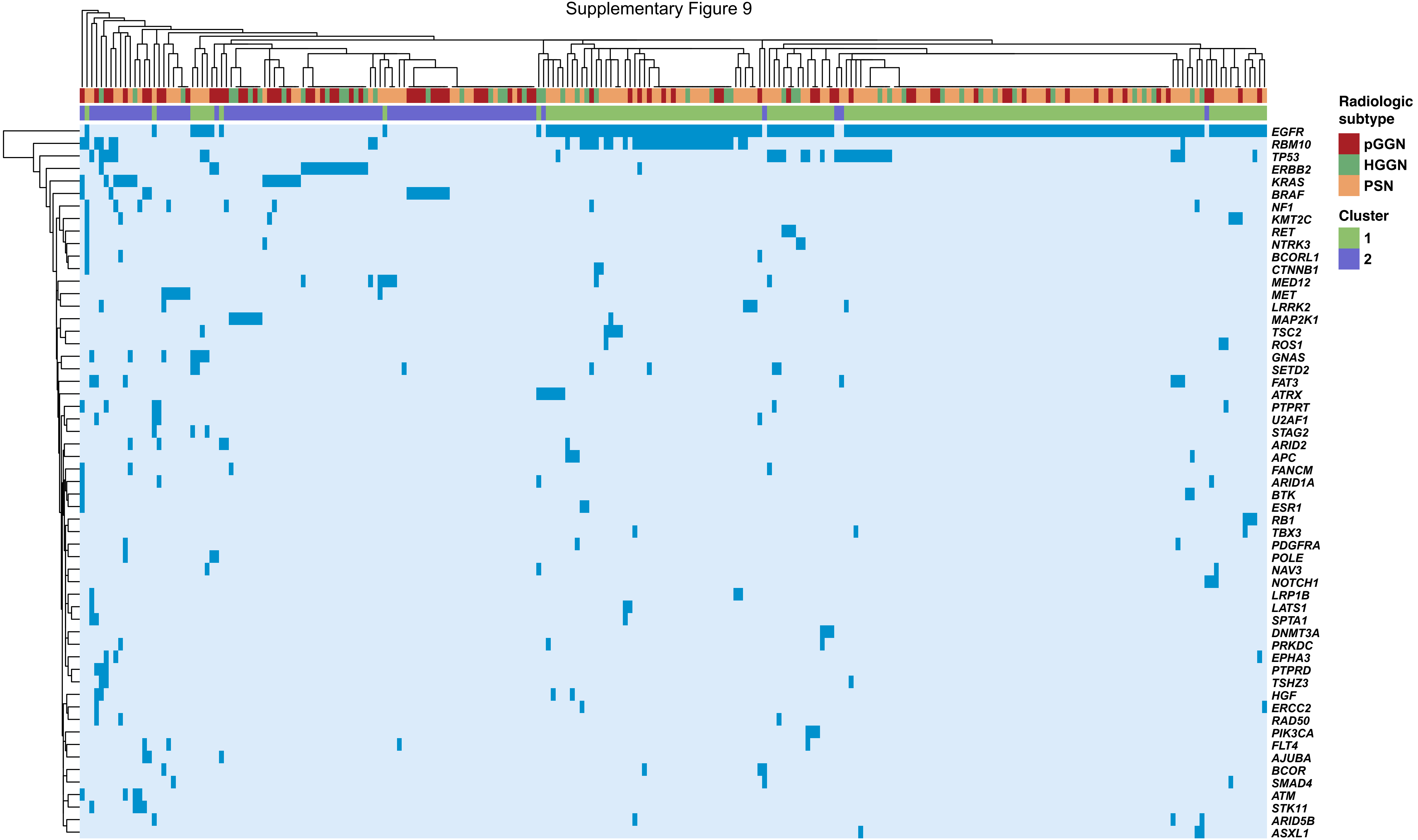
Supplementary Figure 7



Supplementary Figure 8



Supplementary Figure 9



SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure 1. Flow diagram of the broad-panel NGS cohort.

Supplementary Figure 2. Classification of subsolid nodules. (*A*) and (*B*) showed pure ground-glass nodules, which consisted of homogeneous opacities in the lung window. No solid component was observed in the mediastinal window. (*C*) and (*D*) illustrated heterogeneous ground-glass nodules, which harbored a solid component (*black arrow*) in only the lung window but not in the mediastinal window. (*E*) and (*F*) exhibited part-solid nodules, which possessed a solid component both in the lung window (*black arrow*) and in the mediastinal window (*white arrow*).

Supplementary Figure 3. Feature selection with LASSO in the broad-panel NGS cohort. LASSO negative binomial regression model was built incorporating both clinicopathologic characteristics and radiological parameters. (*A*) Red dots indicated average deviance values for each model with a given λ; the dotted vertical lines were drawn at the optimal values using the minimum mean square error (MSE) criteria. The optimal λ value of 0.304 was selected. (*B*) The process of feature selection and resulting features with nonzero coefficients: smoking (0.212), predominant histology (0.124), age (0.008), total size in the lung window (0.005), and solid size in the mediastinal window (0.002). LASSO, least absolute shrinkage and selection operator.

Supplementary Figure 4. Association between radiological subtype and genomic features in the WES cohort. (*A*) Oncoprint of the most frequently mutated genes (top 20) by radiological subtype. (*B*) Box plot of TMB versus radiological subtype. (*C*) Comparison of mutation frequency of top 20 genes among radiological subtypes. Genes with significant differences using Fisher's exact test were labeled with *asterisks* (FDR $q < 0.100$), while those with significant differences in Cochran-Armitage test for trend were highlighted in *red* ($P < 0.050$). TMB, tumor mutational burden.

Supplementary Figure 5. Figure legend: Association between radiological subtype and genomic features in the IAC cohort. (A) Box plot of tumor mutation count versus radiological subtype. (B) Box plot of genomic alteration count versus radiological subtype. (C) Box plot of the MATH score versus radiological subtype. Significant differences were labeled with asterisks ($P < 0.050$). (*D*) Comparison of mutation frequency of driver genes among radiological subtypes. (*E*) Comparison of alteration frequency of oncogenic pathways among radiological subtypes. Significant differences conducted by Fisher's exact test were labeled with *asterisks*, while those calculated by Cochran-Armitage test for trend were highlighted in *red* ($P < 0.050$).

Supplementary Figure 6. Oncogenic pathway analyses in the WES cohort. (*A*) Oncoprint of altered oncogenic pathways by radiological subtype. Pathway alterations were presented by increasing NPA. (*B*) Comparison of alteration frequency of oncogenic pathways among radiological subtypes. Pathways with significant differences using Fisher's exact test were labeled with *asterisks* (FDR $q < 0.100$), while those with significant differences in Cochran-Armitage test for trend were highlighted in *red* ($P < 0.050$). (*C*) Frequency of NPA versus radiological subtype. Darker tones indicate higher alteration frequencies. NPA, number of pathway alteration.

Supplementary Figure 7. Co-occurrence (*red*) and mutual exclusivity (*blue*) analyses of oncogenic pathway in the broad-panel NGS cohort. (*A*), (*B*), (*C*), and (*D*) showed the results in SSN, pGGN, HGGN, and PSN cohorts respectively.

Supplementary Figure 8. Cancer evolution models in (*A*) the broad-panel NGS and (*B*) the WES cohorts detected by CAPRI algorithm. High-frequent somatic mutations were input in the models. The edge label represented relation confidence estimated with 100 non-parametric bootstrap (NPB score) iterations. Edges with $P < 0.050$ were preserved. CAPRI, cancer progression inference.

Supplementary Figure 9. Gene-based somatic mutation clustering analyses in the broad-panel NGS cohort.

Supplementary Tables	**Table S1**	Broad-Panel NGS Gene
	Table S2	Clinicopathologic Characteristics by Radiological Subtype (WES Cohort)
	Table S3	Negative Binomial Regression Analysis on Association with TMB (WES Cohort)
	Table S4	Driver Gene Identification by dNdScv Algorithm
	Table S5	Driver Gene Frequency Comparison between Radiologic Subtypes
	Table S6	Top 20 Gene Frequency Comparison between Radiologic Subtypes (WES Cohort)
	Table S7	Driver Gene Frequency Comparison between Radiologic Subtypes (IAC)
	Table S8	Co-occurrence and Mutual Exclusivity of Driver Gene in the Entire Cohort
	Table S9	Co-occurrence and Mutual Exclusivity of Driver Gene in pGGN Cohort
	Table S10	Co-occurrence and Mutual Exclusivity of Driver Gene in HGGN Cohort
	Table S11	Co-occurrence and Mutual Exclusivity of Driver Gene in PSN Cohort
	Table S12	Pathway Alteration Comparison between Radiologic Subtypes
	Table S13	Pathway Alteration Comparison between Radiologic Subtypes (WES Cohort)
	Table S14	Pathway Alteration Comparison between Radiologic Subtypes (IAC)
	Table S15	Co-occurrence and Mutual Exclusivity of Oncogenic Pathway in the Entire Cohort
	Table S16	Co-occurrence and Mutual Exclusivity of Oncogenic Pathway in pGGN Cohort
	Table S17	Co-occurrence and Mutual Exclusivity of Oncogenic Pathway in HGGN Cohort
	Table S18	Co-occurrence and Mutual Exclusivity of Oncogenic Pathway in PSN Cohort
	Table S19	Mutational Signature (WES Cohort)

Table S1. Broad-Panel NGS Gene

HR363	**HR456**	**RS520**
ABL1	ABL1	ABL1
ACVR1B	ACVR1B	ABL2
ACVR2A	ACVR2A	ACVR1
AJUBA	AJUBA	ACVR1B
AKT1	AKT1	ADGRA2
AKT2	AKT2	AKT1
AKT3	AKT3	AKT2
ALK	ALK	AKT3
AMER1	ALOX12B	ALK
APC	AMER1	ALOX12B
AR	APC	ANKRD11
ARHGAP35	AR	APC

ARHGEF12
ARID1A
ARID2
ARID5B
ASXL1
ATM
ATR
ATRX
AURKA
AURKB
AXIN2
AXL
B2M
B4GALT3
BAGE
BAP1
BARD1
BCL2
BCL2L1
BCL6
BLM
BMPR1A
BRAF
BRCA1
BRCA2
BRIP1
BTK
BTLA
CARD11
CBFB
CBL
CCND1
CCND2
CCNE1
CD160
CD244
CD274
CD276
CD28
CD38
CD48
CD69
CD79B

ARAF
ARFRP1
ARHGAP35
ARHGEF12
ARID1A
ARID2
ARID5B
ASXL1
ATM
ATR
ATRX
AURKA
AURKB
AXIN1
AXIN2
AXL
B2M
B4GALT3
BAGE
BAP1
BARD1
BCL2
BCL2L1
BCL2L2
BCL6
BCOR
BCORL1
BLM
BMPR1A
BRAF
BRCA1
BRCA2
BRD4
BRIP1
BTG1
BTG2
BTK
BTLA
CALR
CARD11
CASP8
CBFB
CBL

AR
ARAF
ARID1A
ARID1B
ARID2
ARID5B
ASXL1
ASXL2
ATF1
ATM
ATR
ATRX
AURKA
AURKB
AXIN1
AXIN2
AXL
B2M
BAP1
BARD1
BCL2
BCL2L1
BCL6
BCOR
BCORL1
BCR
BIRC3
BLM
BMPR1A
BRAF
BRCA1
BRCA2
BRD4
BRIP1
BTK
CARD11
CASP8
CBFB
CBL
CCND1
CCND2
CCND3
CCNE1

CD80
CD86
CDC73
CDH1
CDK12
CDK4
CDK6
CDK8
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CDKN2A
CDKN2B
CDKN2C
CEBPA
CHEK1
CHEK2
CIC
CREBBP
CRIPAK
CRKL
CSF1R
CTAG2
CTCF
CTLA4
CTNNA1
CTNNB1
DAXX
DDR2
DICER1
DNMT3A
EGFR
EGR3
EIF4A2
ELF3
EOMES
EP300
EPCAM
EPHA1
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CCNE1
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CEBPA
CHEK1
CHEK2
CIC
CREBBP
CRIPAK
CRKL
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CTAG2
CTCF
CTLA4
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CTNNB1
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CUL4B
CYLD
DAXX
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DICER1
DNMT1
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DNMT3B
DOT1L
EGFR
EIF4E

ERBB2
ERBB3
ERBB4
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ERCC3
ERCC4
ERCC5
ERG
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ETV1
EZH2
FANCA
FANCC
FANCM
FBXW7
FGF19
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FGF4
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FGFR2
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FGFR4
FH
FLCN
FLT1
FLT3
FLT4
FOXA1
FOXA2
FOXL2
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FRK
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CUL3
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CXCR4
CYP17A1
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DIS3
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FANCL
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FH
FLCN
FLT1

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HDAC2
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HDAC6
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HIST1H1C
HIST1H2BD
HNF1A
HRAS
ICOS
ICOSLG
IDH1
IDH2
IGF1R
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IKBKE
IKZF1
IL7R
INSR
IRF4
IRS2
ITK
JAK1
JAK2
JAK3
JUN
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KDR
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KIT
KITLG
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LCK
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LIFR
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LRRK2

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SDHC
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RARA

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SPATA2
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PDGFRB
PDK1
PHF6
PHOX2B
PIGF
PIK3C2B
PIK3C2G
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PIK3CB
PIK3CD
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PRDM1
PRF1
PRKAR1A
PRKCI
PRX
PTCH1
PTEN
PTK6
PTPN11
PTPRD
PTPRK
PTPRO
PTPRT
QKI
RAC1
RAD21
RASA1
RB1
RBM10
RECQL4
RET
RHOA
RICTOR
RNF43
ROS1
RPS6KA4
RPS6KB2
RPTOR
RUNX1
RUNX1T1
SDHA
SDHB
SDHC
SDHD
SETD2
SF3B1
SH2B3
SLIT2
SLX4
SMAD2
SMAD3
SMAD4
SMARCA4
SMARCB1
SMARCD1
SMO
SNCAIP
SOX9
SPEN
SPOP
SPTA1
SRC
SRSF2
STAG2
STAT3
STAT5A
STAT5B
STK11
STK40

VEGFA	RAD50	SUFU
VEGFB	RAD51	SYK
VEZF1	RAD51B	TAF1
VHL	RAD51C	TBX3
VTCN1	RAD51D	TCF3
WT1	RAD52	TCF7L2
XPO1	RAD54L	TERT
XRCC2	RAF1	TET2
NA	RARA	TGFBR2
NA	RB1	TMPRSS2
NA	RBM10	TNFAIP3
NA	RECQL	TNFRSF14
NA	RECQL4	TNFSF11
NA	REL	TOP1
NA	RET	TP53
NA	RICTOR	TP63
NA	RNF43	TRAF2
NA	ROS1	TRAF7
NA	RPA1	TRRAP
NA	RPA2	TSC1
NA	RPA3	TSC2
NA	RPL22	TSHR
NA	RPL5	U2AF1
NA	RPTOR	VEGFA
NA	RUNX1	VHL
NA	SDHA	WRN
NA	SDHB	WT1
NA	SDHC	XPO1
NA	SDHD	XRCC2
NA	SETBP1	YES1
NA	SETD2	ZFHX3
NA	SF3B1	ZNF217
NA	SGK1	ZNF703
NA	SH2D1A	ZNRF3
NA	SIK1	AMER1
NA	SIN3A	APCDD1
NA	SLAMF7	ARFRP1
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NA	SMARCA4	BCL10
NA	SMARCB1	BCL2L11
NA	SMC1A	BCL2L2
NA	SMC3	BTG1

NA	SMO	CALR
NA	SNCAIP	CD276
NA	SOCS1	CENPA
NA	SOX17	CRBN
NA	SOX2	CTLA4
NA	SOX9	CTNNA1
NA	SPATA2	CXCR4
NA	SPEN	CYP17A1
NA	SPOP	DCUN1D1
NA	SRC	DIS3
NA	STAG2	DNAJB1
NA	STAT3	E2F3
NA	STK11	EED
NA	SUFU	EGFL7
NA	SYK	EIF1AX
NA	TAF1	EIF4A2
NA	TAS2R38	ERCC3
NA	TBL1XR1	ERCC4
NA	TBX3	ERCC5
NA	TEK	FAM46C
NA	TET1	FANCF
NA	TET2	FANCM
NA	TGFB1	FAS
NA	TGFBR2	FGF10
NA	TIPARP	FGF23
NA	TLR4	FGF6
NA	TNF	FGF7
NA	TNFAIP3	FOXA1
NA	TNFRSF14	FOXL2
NA	TNFRSF18	GATA4
NA	TNFRSF4	GID4
NA	TNFSF11	GNA13
NA	TNFSF14	GPS2
NA	TNFSF18	GREM1
NA	TNFSF4	H3F3B
NA	TOP1	H3F3C
NA	TP53	HIST1H1C
NA	TSC1	HIST1H2BD
NA	TSC2	HIST1H3A
NA	TSHR	HIST1H3B
NA	TSHZ2	HIST1H3C
NA	TSHZ3	HIST1H3D
NA	TYRO3	HIST1H3E

NA	U2AF1	HIST1H3G
NA	USP9X	HIST1H3H
NA	VEGFA	HIST1H3I
NA	VEGFB	HIST1H3J
NA	VEZF1	HIST2H3C
NA	VHL	HIST2H3D
NA	VTCN1	HIST3H3
NA	WHSC1	HOXB13
NA	WHSC1L1	HSD3B1
NA	WT1	ICOSLG
NA	XPO1	ID3
NA	XRCC2	IFNGR1
NA	ZNF217	IL10
NA	ZNF703	INHA
NA	NA	IRS1
NA	NA	JUN
NA	NA	KLF4
NA	NA	KLHL6
NA	NA	LYN
NA	NA	LZTR1
NA	NA	MALT1
NA	NA	MAP3K14
NA	NA	MAPK1
NA	NA	MGA
NA	NA	MYOD1
NA	NA	NCOA3
NA	NA	NEGR1
NA	NA	NKX3-1
NA	NA	PARP1
NA	NA	PDCD1
NA	NA	PDCD1LG2
NA	NA	PDK1
NA	NA	PDPK1
NA	NA	PHOX2B
NA	NA	PIK3C2B
NA	NA	PIK3C3
NA	NA	PIK3R3
NA	NA	PLK2
NA	NA	PMAIP1
NA	NA	PNRC1
NA	NA	POM121L12
NA	NA	PPM1D
NA	NA	PRKCI

NA	NA	PRSS8
NA	NA	RAB35
NA	NA	RAD21
NA	NA	RANBP2
NA	NA	REL
NA	NA	RFWD2
NA	NA	RHEB
NA	NA	RIT1
NA	NA	RPA1
NA	NA	RYBP
NA	NA	SDHAF2
NA	NA	SH2D1A
NA	NA	SHQ1
NA	NA	SOCS1
NA	NA	SOX10
NA	NA	SOX17
NA	NA	SOX2
NA	NA	STAT4
NA	NA	SUZ12
NA	NA	TACC3
NA	NA	TERC
NA	NA	TET1
NA	NA	TGFBR1
NA	NA	TIPARP
NA	NA	TMEM127
NA	NA	TOP2A
NA	NA	VEGFB
NA	NA	VEGFC
NA	NA	VTCN1
NA	NA	WISP3
NA	NA	XIAP
NA	NA	XRCC3
NA	NA	YAP1
NA	NA	ZBTB2
NA	NA	ZRSR2

Table S2. Clinicopathologic Characteristics by Radiological Subtype (WES Cohort)

Characteristic	**Total (N=125)**	**pGGN (n=48 [38%])**	**HGGN (n=29 [24%])**	**PSN (n=48 [38%])**	***P* value**
Age at resection, y	60.0 (54.0-65.0)	58.5 (53.5-64.0)	60.0 (54.0-66.0)	61.0 (56.5-68.5)	**0.043**
Sex					
Male	47 (38)	19 (40)	11 (38)	17 (35)	0.914
Female	78 (62)	29 (60)	18 (62)	31 (65)	
Smoking status					
Nonsmoker	93 (74)	38 (80)	20 (69)	35 (73)	0.583
Smoker	32 (26)	10 (20)	9 (31)	13 (27)	
Total size on CT, mm	15.8 (10.9-24.7)	10.8 (7.6-13.9)	17.4 (13.4-21.9)	24.8 (15.7-29.4)	**<0.001**
Procedure type					
Wedge resection	51 (41)	29 (60)	8 (28)	14 (29)	**0.003**
Segmentectomy	9 (7)	4 (9)	3 (10)	2 (4)	
Lobectomy	65 (52)	15 (31)	18 (62)	32 (67)	
Pathological subtype					
AIS	19 (15)	17 (35)	1 (4)	1 (2)	**<0.001**
MIA	25 (20)	21 (45)	3 (10)	1 (2)	
IAC	81 (65)	10 (20)	25 (86)	46 (96)	
Predominant histology					
LEP	69 (55)	42 (88)	15 (52)	12 (25)	**<0.001**
ACI/PAP	56 (45)	6 (12)	14 (48)	36 (75)	
Pathological stage					
0	19 (15)	17 (35)	1 (4)	1 (2)	**<0.001**
IA	98 (78)	31 (65)	28 (96)	39 (81)	
IB	8 (7)	0 (0)	0 (0)	8 (17)	

ACI, acinar; AIS, adenocarcinoma in situ; CT, computed tomography; IAC, invasive adenocarcinoma; LEP, lepidic; MIA, minimally invasive adenocarcinoma; PAP, papillary; WES, whole exome sequencing.

Table S3. Negative Binomial Regression Analysis on Association with TMB (WES Cohort)

	Univariate analysis			Multivariate analysis		
Variable	**IRR**	**95% CI**	***P* value**	**IRR**	**95% CI**	***P* value**
Age at resection, per 1y increased	1.020	1.003 to 1.039	**0.025**	1.013	0.994 to 1.033	0.191
Sex						
Male			Reference			Reference
Female	0.747	0.538 to 1.040	0.082	0.842	0.534 to 1.350	0.467
Smoking						
No			Reference			Reference
Yes	1.418	0.994 to 1.997	**0.049**	1.216	0.756 to 1.970	0.423
Pathological subtype						
AIS			Reference			Reference
MIA	1.528	0.738 to 3.375	0.268	1.435	0.679 to 3.220	0.357
IAC	2.673	1.483 to 5.408	**0.003**	1.854	0.888 to 4.165	0.114
Predominant histology						
LEP			Reference			Reference
ACI/PAP	1.651	1.193 to 2.296	**0.003**	1.172	0.764 to 1.834	0.475
Total size on CT (L), per 1mm increased	1.027	1.012 to 1.042	**<0.001**	1.011	0.982 to 1.039	0.461
Solid size on CT (L), per 1mm increased	1.030	1.013 to 1.047	**<0.001**	0.991	0.939 to 1.043	0.723
Solid size on CT (M), per 1mm increased	1.029	1.010 to 1.047	**0.001**	1.017	0.974 to 1.066	0.478

ACI, acinar; AIS, adenocarcinoma in situ; CT, computed tomography; IAC, invasive adenocarcinoma; IRR, incidence rate ratio; L, Lung window; LEP, lepidic; M, Mediastinal (soft-tissue) window; MIA, minimally invasive adenocarcinoma; PAP, papillary; TMB, tumor mutation burden; WES, whole exome sequencing.

Table S4. Driver Gene Identification by dNdScv Algorithm

Entire Cohort (q < 0.1 and nonsilent mutations n ≥ 5)

gene_name	**n_syn**	**n_mis**	**n_non**	**n_spl**	**n_ind**	**wmis_cv**	**wnon_cv**	**wspl_cv**	**wind_cv**	**pmis_cv**	**ptrunc_cv**	**pallsubs_cv**	**pind_cv**	**qmis_cv**	**qtrunc_cv**	**qallsubs_cv**	**pglobal_cv**	**qglobal_cv**
EGFR	1	97	0	0	32	329.3575	0	0	292.8483	0	0.816405	0	6.48E-18	0	0.99768	0	0	**0**
KRAS	0	15	0	0	0	1034345.79	0	0	0	0	0.985775	0	1	0	0.99768	0	0	**0**
RBM10	0	0	17	2	21	0	26722.21	26722.21	249.9807	0.9912159	0	0	3.86E-14	0.991028	0	0	0	**0**
TP53	2	22	2	1	6	14.057337	20.35841	20.35841	168.7687	5.74E-07	0.001886	1.07E-06	4.31E-07	8.95E-05	0.196515	0.000134	1.36E-11	**2.12E-09**
BRAF	0	13	0	0	1	976.6393	0	0	14.44912	3.73E-08	0.954479	1.62E-07	0.05856	7.74E-06	0.99768	2.52E-05	1.84E-07	**2.30E-05**
MAP2K1	0	0	0	1	4	0	2049.186	2049.186	112.5124	0.9923424	0.004676	0.015663	3.12E-05	0.991028	0.316066	0.424257	7.60E-06	**0.000789**
MED12	0	5	3	0	4	187.0877	1062.381	1062.381	20.3255	0.0072285	0.000148	0.000459	0.0566	0.2547737	0.030834	0.035773	3.60E-05	**0.003207**
ERBB2	3	1	0	0	8	0.4680034	0	0	70.58902	0.4865587	0.551121	0.682304	1.02E-05	0.991028	0.99768	0.999888	8.93E-05	**0.00695**
MET	0	1	1	0	3	151.2613	1714.57	1714.57	23.59647	0.07523	0.005676	0.012934	0.006179	0.574058	0.316066	0.424257	0.000834	**0.057729**

SETD2	0	1	1	0	6	55.854	586.8247	586.8247	25.92392	0.18892	0.018164	0.057056	0.001615	0.803243	0.452651	0.67619	0.000948	**0.05908**
NF1	0	4	1	0	4	207.2803	507.7561	507.7561	15.60912	0.00736	0.021228	0.011105	0.010329	0.254737	0.477497	0.424257	0.001155	**0.065443**
U2AF1	0	4	1	0	0	691.3435	1562.824	1562.824	0	0.000161	0.006277	0.000163	1	0.020059	0.316066	0.016875	0.00158	**0.082052**

pGGN Cohort (q < 0.1 and nonsilent mutations n ≥ 5)

gene_name	**n_syn**	**n_mis**	**n_non**	**n_spl**	**n_ind**	**wmis_cv**	**wnon_cv**	**wspl_cv**	**wind_cv**	**pmis_cv**	**ptrunc_cv**	**pallsubs_cv**	**pind_cv**	**qmis_cv**	**qtrunc_cv**	**qallsubs_cv**	**pglobal_cv**	**qglobal_cv**
EGFR	0	12	0	0	13	371.8761	0	0	416.3936	0	0.932788	2.22E-16	2.15E-29	0	0.998697	1.38E-13	0	**0**
RBM10	0	0	4	0	6	0	533.4681	533.4681	249.9807	0.724852	2.58E-09	1.40E-08	3.62E-13	0.951328	1.61E-06	2.18E-06	0	**0**
KRAS	0	7	0	0	0	690.5132	0	0	0	2.99E-14	0.96459	2.86E-13	1	9.30E-12	0.998697	8.92E-11	8.55E-12	**1.78E-09**
BRAF	0	12	0	0	1	80.5048	0	0	50.57193	1.72E-10	0.84769	1.07E-09	0.019575	3.57E-08	0.998697	2.23E-07	5.38E-10	**8.38E-08**
ERBB2	1	1	0	0	5	2.166573	0	0	154.4135	0.539485	0.758487	0.780366	3.60E-10	0.951328	0.998697	0.999965	6.46E-09	**8.04E-07**
MAP2K1	0	0	0	0	3	0	0	0	295.3452	0.744139	0.913451	0.942549	1.85E-07	0.951328	0.998697	0.999965	2.89E-06	**0.000301**

HGGN Cohort (q < 0.1 and nonsilent mutations n ≥ 5)

gene_name	**n_syn**	**n_mis**	**n_non**	**n_spl**	**n_ind**	**wmis_cv**	**wnon_cv**	**wspl_cv**	**wind_cv**	**pmis_cv**	**ptrunc_cv**	**pallsubs_cv**	**pind_cv**	**qmis_cv**	**qtrunc_cv**	**qallsubs_cv**	**pglobal_cv**	**qglobal_cv**
EGFR	0	18	0	0	9	199.2342	0	0	576.545	5.62E-14	0.907104	3.95E-13	1.62E-22	3.50E-11	0.981359	2.46E-10	0	**0**
RBM10	0	0	5	1	2	0	906.9616	906.9616	166.6538	0.7051553	2.41E-12	6.70E-12	7.16E-05	0.9000551	1.50E-09	2.09E-09	1.74E-14	**5.43E-12**
ERBB2	1	0	0	0	4	0	0	0	247.0616	0.6518819	0.903142	0.89654	2.86E-09	0.9000551	0.981359	0.991681	5.33E-08	**1.11E-05**
MAP2K1	0	0	0	0	3	0	0	0	590.6904	0.8137355	0.950072	0.970721	2.19E-08	0.9000551	0.981359	0.991681	3.97E-07	**6.18E-05**
TP53	0	2	0	0	2	69.33358	0	0	393.7936	0.00078	0.947324	0.003504	1.29E-05	0.161895	0.981359	0.545707	8.08E-07	**0.000101**

PSN Cohort (q < 0.1 and nonsilent mutations n ≥ 5)

gene_name	**n_syn**	**n_mis**	**n_non**	**n_spl**	**n_ind**	**wmis_cv**	**wnon_cv**	**wspl_cv**	**wind_cv**	**pmis_cv**	**ptrunc_cv**	**pallsubs_cv**	**pind_cv**	**qmis_cv**	**qtrunc_cv**	**qallsubs_cv**	**pglobal_cv**	**qglobal_cv**
EGFR	1	67	0	0	22	248.5778	0	0	352.3331	0	0.827962	0	5.40E-16	0	0.994775	0	0	**0**
RBM10	0	0	8	1	13	0	1150.857	1150.857	270.8124	0.6979941	0	0	2.00E-11	0.894471	0	0	0	**0**
TP53	1	17	1	1	4	30.57	36.75	36.75	196.8	2.94E-10	0.002606	5.23E-10	5.61E-06	6.12E-08	0.405837	8.14E-08	1.01E-13	**2.10E-11**

						674	932	932	968									
KRAS	0	6	0	0	0	389.8022	0	0	0	2.90E-11	0.951979	2.44E-10	1	9.04E-09	0.994775	5.07E-08	5.65E-09	**8.79E-07**
MED12	0	3	3	0	4	13.55808	128.2363	128.2363	35.56962	0.013799	2.10E-05	3.80E-05	0.001593	0.538958	0.00655	0.004735	1.07E-06	**0.000133**

Table S5. Driver Gene Frequency Comparison between Radiologic Subtypes (Mutation Frequency > 0.02 were included)

Fisher's Exact Test (pGGN vs. HGGN)

Gene Symbol	**pGGN_mut_num**	**pGGN_nomut_num**	**HGGN_mut_num**	**HGGN_nomut_num**	**total_mutfreq**	**pGGN_mutfreq**	**HGGN_mutfreq**	**mut_dif**	**p_value**	**q_value**
EGFR	34	43	26	22	0.48	0.441558	0.541667	0.100108	0.357568	0.697462
RBM10	10	67	8	40	0.144	0.12987	0.166667	0.036797	0.606702	0.728042
TP53	4	73	4	44	0.064	0.051948	0.083333	0.031385	0.482073	0.697462
ERBB2	10	67	7	41	0.136	0.12987	0.145833	0.015963	0.794801	0.867056
KRAS	7	70	2	46	0.072	0.090909	0.041667	0.049242	0.480372	0.697462
BRAF	12	65	1	47	0.104	0.155844	0.020833	0.135011	0.016313	0.195753
MAP2K1	3	74	4	44	0.056	0.038961	0.083333	0.044372	0.426979	0.697462
MED12	0	77	2	46	0.016	0	0.041667	0.041667	0.145548	0.697462
NF1	3	74	0	48	0.024	0.038961	0	0.038961	0.284645	0.697462
MET	2	75	1	47	0.024	0.025974	0.020833	0.005141	1	1
SETD2	2	75	0	48	0.016	0.025974	0	0.025974	0.523097	0.697462
U2AF1	3	74	0	48	0.024	0.038961	0	0.038961	0.284645	0.697462

Fisher's Exact Test (pGGN vs. PSN)

Gene Symbol	pGGN_mut_num	pGGN_nomut_num	PSN_mut_num	PSN_nomut_num	total_mutfreq	pGGN_mutfreq	PSN_mutfreq	mut_dif	p_value	q_value
EGFR	34	43	96	26	0.653266	0.441558	0.786885	0.345327	8.37E-07	**1.00E-05**
RBM10	10	67	22	100	0.160804	0.12987	0.180328	0.050458	0.429518	0.57269
TP53	4	73	23	99	0.135678	0.051948	0.188525	0.136577	0.005651	**0.0169954**
ERBB2	10	67	1	121	0.055276	0.12987	0.008197	0.121673	0.000383	**0.001534**
KRAS	7	70	6	116	0.065327	0.090909	0.04918	0.041729	0.255401	0.451031
BRAF	12	65	0	122	0.060302	0.155844	0	0.155844	6.40E-06	**3.84E-05**
MAP2K1	3	74	1	121	0.020101	0.038961	0.008197	0.030764	0.300688	0.451031
MED12	0	77	6	116	0.030151	0	0.04918	0.04918	0.083687	0.20085
NF1	3	74	5	117	0.040201	0.038961	0.040984	0.002023	1	1
MET	2	75	4	118	0.030151	0.025974	0.032787	0.006813	1	1
SETD2	2	75	5	117	0.035176	0.025974	0.040984	0.01501	0.708477	0.850172
U2AF1	3	74	1	121	0.020101	0.038961	0.008197	0.030764	0.300688	0.451031

Fisher's Exact Test (HGGN vs. PSN)

Gene Symbol	HGGN_mut_num	HGGN_nomut_num	PSN_mut_num	PSN_nomut_num	total_mutfreq	HGGN_mutfreq	PSN_mutfreq	mut_dif	p_value	q_value
EGFR	26	22	96	26	0.717647	0.541667	0.786885	0.245219	0.002262	**0.01357**
RBM10	8	40	22	100	0.176471	0.166667	0.180328	0.013661	1	1

TP53	4	44	23	99	0.158824	0.083333	0.188525	0.105191	0.106451	0.319354
ERBB2	7	41	1	121	0.047059	0.145833	0.008197	0.137637	0.000639	**0.007674**
KRAS	2	46	6	116	0.047059	0.041667	0.04918	0.007514	1	1
BRAF	1	47	0	122	0.005882	0.020833	0	0.020833	0.282353	0.554091
MAP2K1	4	44	1	121	0.029412	0.083333	0.008197	0.075137	0.022825	**0.091301**
MED12	2	46	6	116	0.047059	0.041667	0.04918	0.007514	1	1
NF1	0	48	5	117	0.029412	0	0.040984	0.040984	0.32322	0.554091
MET	1	47	4	118	0.029412	0.020833	0.032787	0.011954	1	1
SETD2	0	48	5	117	0.029412	0	0.040984	0.040984	0.32322	0.554091
U2AF1	0	48	1	121	0.005882	0	0.008197	0.008197	1	1

Cochran-Armitage Trend Test

Gene Symbol	**pGGN_mut_num**	**pGGN_nomut_num**	**HGGN_mut_num**	**HGGN_nomut_num**	**PSN_mut_num**	**PSN_nomut_num**	**pGGN_mutfreq**	**HGGN_mutfreq**	**PSN_mutfreq**	**p_value**
EGFR	34	43	26	22	96	26	0.441558	0.541667	0.786885	**4.67E-07**
RBM10	10	67	8	40	22	100	0.12987	0.166667	0.180328	0.354406
TP53	4	73	4	44	23	99	0.051948	0.083333	0.188525	**0.003525**
ERBB2	10	67	7	41	1	121	0.12987	0.145833	0.008197	**0.000626**

KRAS	7	70	2	46	6	116	0.090909	0.041667	0.04918	0.257849
BRAF	12	65	1	47	0	122	0.155844	0.020833	0	**3.19E-06**
MAP2K1	3	74	4	44	1	121	0.038961	0.083333	0.008197	0.157387
MED12	0	77	2	46	6	116	0	0.041667	0.04918	0.063222
NF1	3	74	0	48	5	117	0.038961	0	0.040984	0.824427
MET	2	75	1	47	4	118	0.025974	0.020833	0.032787	0.751881
SETD2	2	75	0	48	5	117	0.025974	0	0.040984	0.451795
U2AF1	3	74	0	48	1	121	0.038961	0	0.008197	0.117565

Table S6. Top 20 Gene Frequency Comparison between Radiologic Subtypes (WES Cohort)

Fisher's Exact Test (pGGN vs. HGGN)										
Gene Symbol	**pGGN_mut_num**	**pGGN_nomut_num**	**HGGN_mut_num**	**HGGN_nomut_num**	**total_mutfreq**	**pGGN_mutfreq**	**HGGN_mutfreq**	**mut_dif**	**p_value**	**q_value**
EGFR	18	30	15	14	0.428571	0.375	0.517241	0.142241	0.243767	0.715995
RBM10	3	45	7	22	0.12987	0.0625	0.241379	0.178879	0.035441	0.499522
TP53	3	45	5	24	0.103896	0.0625	0.172414	0.109914	0.144775	0.5791
RYR1	1	47	2	27	0.038961	0.020833	0.068966	0.048132	0.552809	1
STK11	4	44	1	28	0.064935	0.083333	0.034483	0.048851	0.644587	1
BIRC6	3	45	2	27	0.064935	0.0625	0.068966	0.006466	1	1
MUC4	2	46	1	28	0.038961	0.041667	0.034483	0.007184	1	1
CHD2	3	45	0	29	0.038961	0.0625	0	0.0625	0.286398	0.715995
KRAS	2	46	2	27	0.051948	0.041667	0.068966	0.027299	0.629355	1
ARID1B	0	48	2	27	0.025974	0	0.068966	0.068966	0.138756	0.5791
CCDC168	3	45	1	28	0.051948	0.0625	0.034483	0.028017	1	1
CPXM2	1	47	1	28	0.025974	0.020833	0.034483	0.013649	1	1
FLG	3	45	0	29	0.038961	0.0625	0	0.0625	0.286398	0.715995
FRG1	1	47	0	29	0.012987	0.020833	0	0.020833	1	1
HMCN1	0	48	0	29	0	0	0	0	1	1
MUC16	1	47	1	28	0.025974	0.020833	0.034483	0.013649	1	1
PPP2R5A	0	48	3	26	0.038961	0	0.103448	0.103448	0.049952	0.499522
RIMS2	0	48	2	27	0.025974	0	0.068966	0.068966	0.138756	0.5791
RSPO1	1	47	1	28	0.025974	0.020833	0.034483	0.013649	1	1

TTN	1	47	2	27	0.038961	0.020833	0.068966	0.048132	0.552809	1

Fisher's Exact Test (pGGN vs. PSN)

Gene Symbol	pGGN_mut_num	pGGN_nomut_num	PSN_mut_num	PSN_nomut_num	total_mutfreq	pGGN_mutfreq	PSN_mutfreq	mut_dif	p_value	q_value
EGFR	18	30	34	14	0.541667	0.375	0.708333	0.333333	0.001959	**0.039176**
RBM10	3	45	13	35	0.166667	0.0625	0.270833	0.208333	0.011886	0.118857
TP53	3	45	11	37	0.145833	0.0625	0.229167	0.166667	0.040045	0.266969
RYR1	1	47	5	43	0.0625	0.020833	0.104167	0.083333	0.203791	0.691729
STK11	4	44	3	45	0.072917	0.083333	0.0625	0.020833	1	1
BIRC6	3	45	2	46	0.052083	0.0625	0.041667	0.020833	1	1
MUC4	2	46	4	44	0.0625	0.041667	0.083333	0.041667	0.677307	0.967582
CHD2	3	45	3	45	0.0625	0.0625	0.0625	0	1	1
KRAS	2	46	2	46	0.041667	0.041667	0.041667	0	1	1
ARID1B	0	48	3	45	0.03125	0	0.0625	0.0625	0.242105	0.691729
CCDC168	3	45	1	47	0.041667	0.0625	0.020833	0.041667	0.616978	0.949197
CPXM2	1	47	3	45	0.041667	0.020833	0.0625	0.041667	0.616978	0.949197
FLG	3	45	2	46	0.052083	0.0625	0.041667	0.020833	1	1
FRG1	1	47	4	44	0.052083	0.020833	0.083333	0.0625	0.36163	0.904075
HMCN1	0	48	5	43	0.052083	0	0.104167	0.104167	0.056027	0.280136
MUC16	1	47	3	45	0.041667	0.020833	0.0625	0.041667	0.616978	0.949197
PPP2R5A	0	48	2	46	0.020833	0	0.041667	0.041667	0.494737	0.949197
RIMS2	0	48	3	45	0.03125	0	0.0625	0.0625	0.242105	0.691729
RSPO1	1	47	3	45	0.041667	0.020833	0.0625	0.041667	0.616978	0.949197

TTN	1	47	2	46	0.03125	0.020833	0.041667	0.020833	1	1

Fisher's Exact Test (HGGN vs. PSN)

Gene Symbol	HGGN_mut_num	HGGN_nomut_num	PSN_mut_num	PSN_nomut_num	total_mutfreq	HGGN_mutfreq	PSN_mutfreq	mut_dif	p_value	q_value
EGFR	15	14	34	14	0.636364	0.517241	0.708333	0.191092	0.141715	1
RBM10	7	22	13	35	0.25974	0.241379	0.270833	0.029454	1	1
TP53	5	24	11	37	0.207792	0.172414	0.229167	0.056753	0.772728	1
RYR1	2	27	5	43	0.090909	0.068966	0.104167	0.035201	0.704344	1
STK11	1	28	3	45	0.051948	0.034483	0.0625	0.028017	1	1
BIRC6	2	27	2	46	0.051948	0.068966	0.041667	0.027299	0.629355	1
MUC4	1	28	4	44	0.064935	0.034483	0.083333	0.048851	0.644587	1
CHD2	0	29	3	45	0.038961	0	0.0625	0.0625	0.286398	1
KRAS	2	27	2	46	0.051948	0.068966	0.041667	0.027299	0.629355	1
ARID1B	2	27	3	45	0.064935	0.068966	0.0625	0.006466	1	1
CCDC168	1	28	1	47	0.025974	0.034483	0.020833	0.013649	1	1
CPXM2	1	28	3	45	0.051948	0.034483	0.0625	0.028017	1	1
FLG	0	29	2	46	0.025974	0	0.041667	0.041667	0.524265	1
FRG1	0	29	4	44	0.051948	0	0.083333	0.083333	0.290941	1
HMCN1	0	29	5	43	0.064935	0	0.104167	0.104167	0.150376	1
MUC16	1	28	3	45	0.051948	0.034483	0.0625	0.028017	1	1
PPP2R5A	3	26	2	46	0.064935	0.103448	0.041667	0.061782	0.358988	1

RIMS2	2	27	3	45	0.064935	0.068966	0.0625	0.006466	1	1
RSPO1	1	28	3	45	0.051948	0.034483	0.0625	0.028017	1	1
TTN	2	27	2	46	0.051948	0.068966	0.041667	0.027299	0.629355	1

Cochran-Armitage Trend Test

Gene Symbol	pGGN_mut_num	pGGN_nomut_num	HGGN_mut_num	HGGN_nomut_num	PSN_mut_num	PSN_nomut_num	pGGN_mutfreq	HGGN_mutfreq	PSN_mutfreq	p_value
EGFR	18	30	15	14	34	14	0.375	0.517241	0.708333	**0.001059**
RBM10	3	45	7	22	13	35	0.0625	0.241379	0.270833	**0.008439**
TP53	3	45	5	24	11	37	0.0625	0.172414	0.229167	**0.022952**
RYR1	1	47	2	27	5	43	0.020833	0.068966	0.104167	0.095315
STK11	4	44	1	28	3	45	0.083333	0.034483	0.0625	0.676678
BIRC6	3	45	2	27	2	46	0.0625	0.068966	0.041667	0.657115
MUC4	2	46	1	28	4	44	0.041667	0.034483	0.083333	0.374649
CHD2	3	45	0	29	3	45	0.0625	0	0.0625	1
KRAS	2	46	2	27	2	46	0.041667	0.068966	0.041667	1
ARID1B	0	48	2	27	3	45	0	0.068966	0.0625	0.11817
CCDC168	3	45	1	28	1	47	0.0625	0.034483	0.020833	0.297566
CPXM2	1	47	1	28	3	45	0.020833	0.034483	0.0625	0.297566
FLG	3	45	0	29	2	46	0.0625	0	0.041667	0.602483
FRG1	1	47	0	29	4	44	0.020833	0	0.083333	0.11817
HMCN1	0	48	0	29	5	43	0	0	0.104167	**0.00921**
MUC16	1	47	1	28	3	45	0.020833	0.034483	0.0625	0.297566
PPP2R5A	0	48	3	26	2	46	0	0.103448	0.041667	0.297566

RIMS2	0	48	2	27	3	45	0	0.068966	0.0625	0.11817
RSPO1	1	47	1	28	3	45	0.020833	0.034483	0.0625	0.297566
TTN	1	47	2	27	2	46	0.020833	0.068966	0.041667	0.602483

Table S7. Driver Gene Frequency Comparison between Radiologic Subtypes (IAC)

Fisher's Exact Test (pGGN vs. HGGN)

Gene Symbol	**pGGN_mut_num**	**pGGN_nomut_num**	**HGGN_mut_num**	**HGGN_nomut_num**	**total_mutfreq**	**pGGN_mutfreq**	**HGGN_mutfreq**	**mut_dif**	**p_value**	**q_value**
EGFR	21	10	21	10	0.67741935	0.67741935	0.67741935	0	1	1
RBM10	6	25	6	25	0.19354839	0.19354839	0.19354839	0	1	1
TP53	2	29	4	27	0.09677419	0.06451613	0.12903226	0.06451613	0.67132683	1
ERBB2	1	30	2	29	0.0483871	0.03225806	0.06451613	0.03225806	1	1
KRAS	6	25	2	29	0.12903226	0.19354839	0.06451613	0.12903226	0.25540587	1
BRAF	1	30	1	30	0.03225806	0.03225806	0.03225806	0	1	1
MAP2K1	1	30	1	30	0.03225806	0.03225806	0.03225806	0	1	1
MED12	0	31	1	30	0.01612903	0	0.03225806	0.03225806	1	1
NF1	1	30	0	31	0.01612903	0.03225806	0	0.03225806	1	1
MET	0	31	0	31	0	0	0	0	1	1
SETD2	1	30	0	31	0.01612903	0.03225806	0	0.03225806	1	1
U2AF1	3	28	0	31	0.0483871	0.09677419	0	0.09677419	0.23770492	1

Fisher's Exact Test (pGGN vs. PSN)

Gene Symbol	**pGGN_mut_num**	**pGGN_nomut_num**	**PSN_mut_num**	**PSN_nomut_num**	**total_mutfreq**	**pGGN_mutfreq**	**PSN_mutfreq**	**mut_dif**	**p_value**	**q_value**
EGFR	21	10	94	21	0.78767123	0.67741935	0.8173913	0.13997195	0.13515397	0.40546191
RBM10	6	25	20	95	0.17808219	0.19354839	0.17391304	0.01963534	0.79459189	1
TP53	2	29	23	92	0.17123288	0.06451613	0.2	0.13548387	0.10585	0.40546191
ERBB2	1	30	1	114	0.01369863	0.03225806	0.00869565	0.02356241	0.38072744	0.65267562

KRAS	6	25	6	109	0.08219178	0.19354839	0.05217391	0.14137447	**0.02059624**	0.18114762
BRAF	1	30	0	115	0.00684932	0.03225806	0	0.03225806	0.21232877	0.50958904
MAP2K1	1	30	1	114	0.01369863	0.03225806	0.00869565	0.02356241	0.38072744	0.65267562
MED12	0	31	4	111	0.02739726	0	0.03478261	0.03478261	0.57861077	0.86791615
NF1	1	30	5	110	0.04109589	0.03225806	0.04347826	0.0112202	1	1
MET	0	31	3	112	0.02054795	0	0.02608696	0.02608696	1	1
SETD2	1	30	5	110	0.04109589	0.03225806	0.04347826	0.0112202	1	1
U2AF1	3	28	1	114	0.02739726	0.09677419	0.00869565	0.08807854	**0.03019127**	0.18114762

Fisher's Exact Test (HGGN vs. PSN)

Gene Symbol	HGGN_mut_num	HGGN_nomut_num	PSN_mut_num	PSN_nomut_num	total_mutfreq	HGGN_mutfreq	PSN_mutfreq	mut_dif	p_value	q_value
EGFR	21	10	94	21	0.78767123	0.67741935	0.8173913	0.13997195	0.13515397	0.81092381
RBM10	6	25	20	95	0.17808219	0.19354839	0.17391304	0.01963534	0.79459189	1
TP53	4	27	23	92	0.18493151	0.12903226	0.2	0.07096774	0.444145	1
ERBB2	2	29	1	114	0.02054795	0.06451613	0.00869565	0.05582048	0.11409621	0.81092381
KRAS	2	29	6	109	0.05479452	0.06451613	0.05217391	0.01234222	0.677579	1
BRAF	1	30	0	115	0.00684932	0.03225806	0	0.03225806	0.21232877	0.84931507
MAP2K1	1	30	1	114	0.01369863	0.03225806	0.00869565	0.02356241	0.38072744	1

MED12	1	30	4	111	0.03424658	0.03225806	0.03478261	0.00252454	1	1
NF1	0	31	5	110	0.03424658	0	0.04347826	0.04347826	0.58454583	1
MET	0	31	3	112	0.02054795	0	0.02608696	0.02608696	1	1
SETD2	0	31	5	110	0.03424658	0	0.04347826	0.04347826	0.58454583	1
U2AF1	0	31	1	114	0.00684932	0	0.00869565	0.00869565	1	1

Cochran-Armitage Trend Test

Gene Symbol	**pGGN_mut_num**	**pGGN_nomut_num**	**HGGN_mut_num**	**HGGN_nomut_num**	**PSN_mut_num**	**PSN_nomut_num**	**pGGN_mutfreq**	**HGGN_mutfreq**	**PSN_mutfreq**	**p_value**
EGFR	21	10	21	10	94	21	0.67741935	0.67741935	0.8173913	0.0516617 1
RBM10	6	25	6	25	20	95	0.19354839	0.19354839	0.17391304	0.7647516
TP53	2	29	4	27	23	92	0.06451613	0.12903226	0.2	0.0577003 8
ERBB2	1	30	2	29	1	114	0.03225806	0.06451613	0.00869565	0.2150450 8
KRAS	6	25	2	29	6	109	0.19354839	0.06451613	0.05217391	**0.0168683 1**
BRAF	1	30	1	30	0	115	0.03225806	0.03225806	0	0.0734529 1
MAP2K1	1	30	1	30	1	114	0.03225806	0.03225806	0.00869565	0.2843409 8
MED12	0	31	1	30	4	111	0	0.03225806	0.03478261	0.3404568 3
NF1	1	30	0	31	5	110	0.03225806	0	0.04347826	0.5364463 6
MET	0	31	0	31	3	112	0	0	0.02608696	0.2358879 1

SETD2	1	30	0	31	5	110	0.03225806	0	0.04347826	0.53644636
U2AF1	3	28	0	31	1	114	0.09677419	0	0.00869565	**0.01089522**

Table S8. Co-occurrence and Mutual Exclusivity of Driver Gene in the Entire Cohort

gene1	**gene2**	**pValue**	**oddsRatio**	**0**	**11**	**1**	**10**	**Event**	**pair**	**event_ratio**
KRAS	EGFR	1.42E-07	0	76	0	156	15	Mutually_Exclusive	EGFR, KRAS	0/171
EGFR	BRAF	1.29E-06	0	78	0	13	156	Mutually_Exclusive	BRAF, EGFR	0/169
ERBB2	EGFR	3.44E-06	0.061524	75	2	154	16	Mutually_Exclusive	EGFR, ERBB2	2/170
MET	EGFR	0.000792	0	84	0	156	7	Mutually_Exclusive	EGFR, MET	0/163
MAP2K1	EGFR	0.004398	0.078145	84	1	155	7	Mutually_Exclusive	EGFR, MAP2K1	1/162
RBM10	EGFR	0.00668	3.205901	84	33	123	7	Co_Occurence	EGFR, RBM10	33/130
NF1	KRAS	0.078037	5.713022	226	2	13	6	Co_Occurence	KRAS, NF1	2/19
EGFR	TP53	0.110057	2.17553	84	24	7	132	Co_Occurence	EGFR, TP53	24/139
NF1	RBM10	0.122839	3.253973	202	3	37	5	Co_Occurence	NF1, RBM10	3/42
EGFR	MED12	0.148543	0.338828	86	3	5	153	Mutually_Exclusive	EGFR, MED12	3/158
EGFR	NF1	0.148543	0.338828	86	3	5	153	Mutually_Exclusive	EGFR, NF1	3/158
MET	MED12	0.20814	5.465339	233	1	7	6	Co_Occurence	MED12, MET	1/13
MET	NF1	0.20814	5.465339	233	1	7	6	Co_Occurence	MET, NF1	1/13
SETD2	NF1	0.20814	5.465339	233	1	7	6	Co_Occurence	NF1, SETD2	1/13
SETD2	TP53	0.214574	2.892558	211	2	29	5	Co_Occurence	SETD2, TP53	2/34
SETD2	EGFR	0.26593	3.585399	90	6	150	1	Co_Occurence	EGFR, SETD2	6/151
SETD2	RBM10	0.316738	2.118239	202	2	38	5	Co_Occurence	RBM10, SETD2	2/43
MED12	ERBB2	0.459053	1.859618	222	1	17	7	Co_Occurence	ERBB2, MED12	1/24
RBM10	U2AF1	0.509054	1.73893	204	1	3	39	Co_Occurence	RBM10, U2AF1	1/42
BRAF	KRAS	0.566394	1.307931	220	1	14	12	Co_Occurence	BRAF, KRAS	1/26

TP53	MAP2K1	0.600849	0	208	0	8	31	Mutually_Exclusive	MAP2K1, TP53	0/39
TP53	MET	0.600849	0	209	0	7	31	Mutually_Exclusive	MET, TP53	0/38
RBM10	MET	0.602259	0	200	0	7	40	Mutually_Exclusive	MET, RBM10	0/47
BRAF	ERBB2	0.607008	0	216	0	18	13	Mutually_Exclusive	BRAF, ERBB2	0/31
ERBB2	KRAS	0.610172	0	214	0	15	18	Mutually_Exclusive	ERBB2, KRAS	0/33
MED12	RBM10	0.619305	1.758363	201	2	38	6	Co_Occurence	MED12, RBM10	2/44
U2AF1	EGFR	0.626844	0.579298	89	2	154	2	Mutually_Exclusive	EGFR, U2AF1	2/156
ERBB2	TP53	0.708773	0.391283	199	1	30	17	Mutually_Exclusive	ERBB2, TP53	1/47
ERBB2	RBM10	0.745559	0.629327	191	2	38	16	Mutually_Exclusive	ERBB2, RBM10	2/54
TP53	RBM10	0.795342	0.741583	180	4	36	27	Mutually_Exclusive	RBM10, TP53	4/63
MET	ERBB2	1	0	222	0	18	7	Mutually_Exclusive	ERBB2, MET	0/25
SETD2	ERBB2	1	0	222	0	18	7	Mutually_Exclusive	ERBB2, SETD2	0/25
U2AF1	ERBB2	1	0	225	0	18	4	Mutually_Exclusive	ERBB2, U2AF1	0/22
MAP2K1	KRAS	1	0	224	0	15	8	Mutually_Exclusive	KRAS, MAP2K1	0/23
MED12	KRAS	1	0	224	0	15	8	Mutually_Exclusive	KRAS, MED12	0/23
RBM10	BRAF	1	0.938014	196	2	11	38	Mutually_Exclusive	BRAF, RBM10	2/49
MET	BRAF	1	0	227	0	13	7	Mutually_Exclusive	BRAF, MET	0/20
SETD2	BRAF	1	0	227	0	13	7	Mutually_Exclusive	BRAF, SETD2	0/20
MED12	MAP2K1	1	0	231	0	8	8	Mutually_Exclusive	MAP2K1, MED12	0/16
NF1	MAP2K1	1	0	231	0	8	8	Mutually_Exclusive	MAP2K1, NF1	0/16
U2AF1	MAP2K1	1	0	235	0	8	4	Mutually_Exclusive	MAP2K1, U2AF1	0/12
NF1	MED12	1	0	231	0	8	8	Mutually_Exclusive	MED12, NF1	0/16

U2AF1	MED12	1	0	235	0	8	4	Mutually_Exclusive	MED12, U2AF1	0/12
U2AF1	NF1	1	0	235	0	8	4	Mutually_Exclusive	NF1, U2AF1	0/12
TP53	U2AF1	1	0	212	0	4	31	Mutually_Exclusive	TP53, U2AF1	0/35
BRAF	U2AF1	1	0	230	0	4	13	Mutually_Exclusive	BRAF, U2AF1	0/17
KRAS	RBM10	1	0.786141	194	2	38	13	Mutually_Exclusive	KRAS, RBM10	2/51
MAP2K1	RBM10	1	0.733437	200	1	39	7	Mutually_Exclusive	MAP2K1, RBM10	1/46
KRAS	TP53	1	1.076611	203	2	29	13	Co_Occurence	KRAS, TP53	2/42
BRAF	TP53	1	0.567743	204	1	30	12	Mutually_Exclusive	BRAF, TP53	1/42
MED12	TP53	1	0.995257	209	1	30	7	Mutually_Exclusive	MED12, TP53	1/37
NF1	TP53	1	0.995257	209	1	30	7	Mutually_Exclusive	NF1, TP53	1/37
MAP2K1	ERBB2	1	0	221	0	18	8	Mutually_Exclusive	ERBB2, MAP2K1	0/26
NF1	ERBB2	1	0	221	0	18	8	Mutually_Exclusive	ERBB2, NF1	0/26
MET	KRAS	1	0	225	0	15	7	Mutually_Exclusive	KRAS, MET	0/22
SETD2	KRAS	1	0	225	0	15	7	Mutually_Exclusive	KRAS, SETD2	0/22
U2AF1	KRAS	1	0	228	0	15	4	Mutually_Exclusive	KRAS, U2AF1	0/19
MAP2K1	BRAF	1	0	226	0	13	8	Mutually_Exclusive	BRAF, MAP2K1	0/21
MED12	BRAF	1	0	226	0	13	8	Mutually_Exclusive	BRAF, MED12	0/21
NF1	BRAF	1	0	226	0	13	8	Mutually_Exclusive	BRAF, NF1	0/21
MET	MAP2K1	1	0	232	0	8	7	Mutually_Exclusive	MAP2K1, MET	0/15
SETD2	MAP2K1	1	0	232	0	8	7	Mutually_Exclusive	MAP2K1, SETD2	0/15
SETD2	MED12	1	0	232	0	8	7	Mutually_Exclusive	MED12, SETD2	0/15
SETD2	MET	1	0	233	0	7	7	Mutually_Exclusive	MET, SETD2	0/14

U2AF1	MET	1	0	236	0	7	4	Mutually_Exclusive	MET, U2AF1	0/11
U2AF1	SETD2	1	0	236	0	7	4	Mutually_Exclusive	SETD2, U2AF1	0/11

Table S9. Co-occurrence and Mutual Exclusivity of Driver Gene in pGGN Cohort

gene1	gene2	pValue	oddsRatio	0	11	1	10	Event	pair	event_ratio
EGFR	BRAF	0.000767	0	31	0	12	34	Mutually_Exclusive	BRAF, EGFR	0/46
RBM10	SETD2	0.015379	Inf	67	2	0	8	Co_Occurence	RBM10, SETD2	2/8
KRAS	EGFR	0.015637	0	36	0	34	7	Mutually_Exclusive	EGFR, KRAS	0/41
NF1	SETD2	0.076897	30.00147	73	1	1	2	Co_Occurence	NF1, SETD2	1/3
RBM10	EGFR	0.096867	3.401013	40	7	27	3	Co_Occurence	EGFR, RBM10	7/30
ERBB2	EGFR	0.171024	0.277594	35	2	32	8	Mutually_Exclusive	EGFR, ERBB2	2/40
SETD2	EGFR	0.191729	Inf	43	2	32	0	Co_Occurence	EGFR, SETD2	2/32
MAP2K1	EGFR	0.250513	0	40	0	34	3	Mutually_Exclusive	EGFR, MAP2K1	0/37
KRAS	NF1	0.251675	5.438548	68	1	2	6	Co_Occurence	KRAS, NF1	1/8
TP53	KRAS	0.322462	3.622946	67	1	6	3	Co_Occurence	KRAS, TP53	1/9
NF1	RBM10	0.345113	3.522404	65	1	9	2	Co_Occurence	NF1, RBM10	1/11
U2AF1	RBM10	0.345113	3.522404	65	1	9	2	Co_Occurence	RBM10, U2AF1	1/11
BRAF	ERBB2	0.346643	0	55	0	10	12	Mutually_Exclusive	BRAF, ERBB2	0/22
RBM10	TP53	0.433611	2.33571	64	1	3	9	Co_Occurence	RBM10, TP53	1/12
TP53	BRAF	0.499703	1.860275	62	1	11	3	Co_Occurence	BRAF, TP53	1/14
MET	EGFR	0.500342	0	41	0	34	2	Mutually_Exclusive	EGFR, MET	0/36
KRAS	ERBB2	0.585016	0	60	0	10	7	Mutually_Exclusive	ERBB2, KRAS	0/17
EGFR	TP53	0.625661	0.408402	40	1	3	33	Mutually_Exclusive	EGFR, TP53	1/36
BRAF	RBM10	0.650316	1.417855	57	2	8	10	Co_Occurence	BRAF, RBM10	2/18
NF1	EGFR	1	0.624913	41	1	33	2	Mutually_Exclusive	EGFR, NF1	1/35

U2AF1	EGFR	1	0.624913	41	1	33	2	Mutually_Exclusive	EGFR, U2AF1	1/35
MAP2K1	TP53	1	0	70	0	4	3	Mutually_Exclusive	MAP2K1, TP53	0/7
NF1	TP53	1	0	70	0	4	3	Mutually_Exclusive	NF1, TP53	0/7
U2AF1	TP53	1	0	70	0	4	3	Mutually_Exclusive	TP53, U2AF1	0/7
RBM10	KRAS	1	1.127811	61	1	6	9	Co_Occurence	KRAS, RBM10	1/15
BRAF	KRAS	1	0.895201	59	1	6	11	Mutually_Exclusive	BRAF, KRAS	1/17
KRAS	MAP2K1	1	0	67	0	3	7	Mutually_Exclusive	KRAS, MAP2K1	0/10
BRAF	MAP2K1	1	0	62	0	3	12	Mutually_Exclusive	BRAF, MAP2K1	0/15
BRAF	NF1	1	0	62	0	3	12	Mutually_Exclusive	BRAF, NF1	0/15
KRAS	MET	1	0	68	0	2	7	Mutually_Exclusive	KRAS, MET	0/9
MAP2K1	MET	1	0	72	0	2	3	Mutually_Exclusive	MAP2K1, MET	0/5
NF1	MET	1	0	72	0	2	3	Mutually_Exclusive	MET, NF1	0/5
U2AF1	MET	1	0	72	0	2	3	Mutually_Exclusive	MET, U2AF1	0/5
KRAS	SETD2	1	0	68	0	2	7	Mutually_Exclusive	KRAS, SETD2	0/9
MAP2K1	SETD2	1	0	72	0	2	3	Mutually_Exclusive	MAP2K1, SETD2	0/5
U2AF1	SETD2	1	0	72	0	2	3	Mutually_Exclusive	SETD2, U2AF1	0/5
KRAS	U2AF1	1	0	67	0	3	7	Mutually_Exclusive	KRAS, U2AF1	0/10
BRAF	U2AF1	1	0	62	0	3	12	Mutually_Exclusive	BRAF, U2AF1	0/15
ERBB2	RBM10	1	0.718886	58	1	9	9	Mutually_Exclusive	ERBB2, RBM10	1/18
MAP2K1	RBM10	1	0	64	0	10	3	Mutually_Exclusive	MAP2K1, RBM10	0/13
MET	RBM10	1	0	65	0	10	2	Mutually_Exclusive	MET, RBM10	0/12
ERBB2	TP53	1	0	63	0	4	10	Mutually_Exclusive	ERBB2, TP53	0/14

MET	TP53	1	0	71	0	4	2	Mutually_Exclusive	MET, TP53	0/6
SETD2	TP53	1	0	71	0	4	2	Mutually_Exclusive	SETD2, TP53	0/6
MAP2K1	ERBB2	1	0	64	0	10	3	Mutually_Exclusive	ERBB2, MAP2K1	0/13
NF1	ERBB2	1	0	64	0	10	3	Mutually_Exclusive	ERBB2, NF1	0/13
MET	ERBB2	1	0	65	0	10	2	Mutually_Exclusive	ERBB2, MET	0/12
SETD2	ERBB2	1	0	65	0	10	2	Mutually_Exclusive	ERBB2, SETD2	0/12
U2AF1	ERBB2	1	0	64	0	10	3	Mutually_Exclusive	ERBB2, U2AF1	0/13
MET	BRAF	1	0	63	0	12	2	Mutually_Exclusive	BRAF, MET	0/14
SETD2	BRAF	1	0	63	0	12	2	Mutually_Exclusive	BRAF, SETD2	0/14
NF1	MAP2K1	1	0	71	0	3	3	Mutually_Exclusive	MAP2K1, NF1	0/6
U2AF1	MAP2K1	1	0	71	0	3	3	Mutually_Exclusive	MAP2K1, U2AF1	0/6
U2AF1	NF1	1	0	71	0	3	3	Mutually_Exclusive	NF1, U2AF1	0/6
SETD2	MET	1	0	73	0	2	2	Mutually_Exclusive	MET, SETD2	0/4

Table S10. Co-occurrence and Mutual Exclusivity of Driver Gene in HGGN Cohort.

gene1	gene2	pValue	oddsRatio	0	11	1	10	Event	pair	event_ratio
ERBB2	EGFR	0.002316	0	15	0	26	7	Mutually_Exclusive	EGFR, ERBB2	0/33
EGFR	MAP2K1	0.037594	0	18	0	4	26	Mutually_Exclusive	EGFR, MAP2K1	0/30
EGFR	KRAS	0.204787	0	20	0	2	26	Mutually_Exclusive	EGFR, KRAS	0/28
RBM10	EGFR	0.26029	2.935722	20	6	20	2	Co_Occurence	EGFR, RBM10	6/22
MED12	ERBB2	0.27305	6.248816	40	1	6	1	Co_Occurence	ERBB2, MED12	1/7
MED12	RBM10	0.308511	5.278088	39	1	7	1	Co_Occurence	MED12, RBM10	1/8
EGFR	BRAF	0.458333	0	21	0	1	26	Mutually_Exclusive	BRAF, EGFR	0/27
EGFR	MET	0.458333	0	21	0	1	26	Mutually_Exclusive	EGFR, MET	0/27
TP53	ERBB2	0.479546	2.070908	38	1	6	3	Co_Occurence	ERBB2, TP53	1/9
RBM10	TP53	0.530322	1.737862	37	1	3	7	Co_Occurence	RBM10, TP53	1/10
TP53	EGFR	0.614169	2.686965	21	3	23	1	Co_Occurence	EGFR, TP53	3/24
MED12	KRAS	1	0	44	0	2	2	Mutually_Exclusive	KRAS, MED12	0/4
ERBB2	BRAF	1	0	40	0	1	7	Mutually_Exclusive	BRAF, ERBB2	0/8
RBM10	MAP2K1	1	0	36	0	4	8	Mutually_Exclusive	MAP2K1, RBM10	0/12
ERBB2	MET	1	0	40	0	1	7	Mutually_Exclusive	ERBB2, MET	0/8
MED12	EGFR	1	0.843073	21	1	25	1	Mutually_Exclusive	EGFR, MED12	1/26
ERBB2	RBM10	1	0.812919	34	1	7	6	Mutually_Exclusive	ERBB2, RBM10	1/13
KRAS	RBM10	1	0	38	0	8	2	Mutually_Exclusive	KRAS, RBM10	0/10
BRAF	RBM10	1	0	39	0	8	1	Mutually_Exclusive	BRAF, RBM10	0/9
MET	RBM10	1	0	39	0	8	1	Mutually_Exclusive	MET, RBM10	0/9

KRAS	TP53	1	0	42	0	4	2	Mutually_Exclusive	KRAS, TP53	0/6
BRAF	TP53	1	0	43	0	4	1	Mutually_Exclusive	BRAF, TP53	0/5
MAP2K1	TP53	1	0	40	0	4	4	Mutually_Exclusive	MAP2K1, TP53	0/8
MED12	TP53	1	0	42	0	4	2	Mutually_Exclusive	MED12, TP53	0/6
MET	TP53	1	0	43	0	4	1	Mutually_Exclusive	MET, TP53	0/5
KRAS	ERBB2	1	0	39	0	7	2	Mutually_Exclusive	ERBB2, KRAS	0/9
MAP2K1	ERBB2	1	0	37	0	7	4	Mutually_Exclusive	ERBB2, MAP2K1	0/11
BRAF	KRAS	1	0	45	0	2	1	Mutually_Exclusive	BRAF, KRAS	0/3
MAP2K1	KRAS	1	0	42	0	2	4	Mutually_Exclusive	KRAS, MAP2K1	0/6
MET	KRAS	1	0	45	0	2	1	Mutually_Exclusive	KRAS, MET	0/3
MAP2K1	BRAF	1	0	43	0	1	4	Mutually_Exclusive	BRAF, MAP2K1	0/5
MED12	BRAF	1	0	45	0	1	2	Mutually_Exclusive	BRAF, MED12	0/3
MET	BRAF	1	0	46	0	1	1	Mutually_Exclusive	BRAF, MET	0/2
MED12	MAP2K1	1	0	42	0	4	2	Mutually_Exclusive	MAP2K1, MED12	0/6
MET	MAP2K1	1	0	43	0	4	1	Mutually_Exclusive	MAP2K1, MET	0/5
MET	MED12	1	0	45	0	2	1	Mutually_Exclusive	MED12, MET	0/3

Table S11. Co-occurrence and Mutual Exclusivity of Driver Gene in PSN Cohort.

gene1	**gene2**	**pValue**	**oddsRatio**	**0**	**11**	**1**	**10**	**Event**	**pair**	**event_ratio**
KRAS	EGFR	5.70E-05	0	20	0	96	6	Mutually_Exclusive	EGFR, KRAS	0/102
MET	EGFR	0.001702	0	22	0	96	4	Mutually_Exclusive	EGFR, MET	0/100
EGFR	MED12	0.018485	0.119935	22	2	4	94	Mutually_Exclusive	EGFR, MED12	2/98
EGFR	NF1	0.064437	0.166494	23	2	3	94	Mutually_Exclusive	EGFR, NF1	2/97
MET	NF1	0.15594	9.061337	114	1	4	3	Co_Occurence	MET, NF1	1/7
RBM10	EGFR	0.156564	3.134555	24	20	76	2	Co_Occurence	EGFR, RBM10	20/78
MAP2K1	RBM10	0.180328	Inf	100	1	21	0	Co_Occurence	MAP2K1, RBM10	1/21
MED12	MET	0.184797	7.255076	113	1	3	5	Co_Occurence	MED12, MET	1/8
EGFR	ERBB2	0.213115	0	25	0	1	96	Mutually_Exclusive	EGFR, ERBB2	0/97
NF1	RBM10	0.220628	3.191895	97	2	20	3	Co_Occurence	NF1, RBM10	2/23
NF1	KRAS	0.226248	5.4435	112	1	5	4	Co_Occurence	KRAS, NF1	1/9
SETD2	TP53	0.237275	3.011054	96	2	21	3	Co_Occurence	SETD2, TP53	2/24
TP53	RBM10	0.243292	0.378628	79	2	20	21	Mutually_Exclusive	RBM10, TP53	2/41
EGFR	TP53	0.399779	2.007438	23	20	3	76	Co_Occurence	EGFR, TP53	20/79
RBM10	SETD2	0.58383	0	95	0	5	22	Mutually_Exclusive	RBM10, SETD2	0/27
MAP2K1	EGFR	1	Inf	26	1	95	0	Co_Occurence	EGFR, MAP2K1	1/95
SETD2	EGFR	1	1.08623	25	4	92	1	Co_Occurence	EGFR, SETD2	4/93
U2AF1	EGFR	1	Inf	26	1	95	0	Co_Occurence	EGFR, U2AF1	1/95
NF1	TP53	1	1.078867	95	1	22	4	Co_Occurence	NF1, TP53	1/26
TP53	KRAS	1	0.855599	94	1	5	22	Mutually_Exclusive	KRAS, TP53	1/27

TP53	MED12	1	0.855599	94	1	5	22	Mutually_Exclusive	MED12, TP53	1/27
KRAS	MET	1	0	112	0	4	6	Mutually_Exclusive	KRAS, MET	0/10
MET	SETD2	1	0	113	0	5	4	Mutually_Exclusive	MET, SETD2	0/9
ERBB2	RBM10	1	0	99	0	22	1	Mutually_Exclusive	ERBB2, RBM10	0/23
KRAS	RBM10	1	0.905483	95	1	21	5	Mutually_Exclusive	KRAS, RBM10	1/26
MED12	RBM10	1	0.905483	95	1	21	5	Mutually_Exclusive	MED12, RBM10	1/26
MET	RBM10	1	0	96	0	22	4	Mutually_Exclusive	MET, RBM10	0/26
U2AF1	RBM10	1	0	99	0	22	1	Mutually_Exclusive	RBM10, U2AF1	0/23
ERBB2	TP53	1	0	98	0	23	1	Mutually_Exclusive	ERBB2, TP53	0/24
MAP2K1	TP53	1	0	98	0	23	1	Mutually_Exclusive	MAP2K1, TP53	0/24
MET	TP53	1	0	95	0	23	4	Mutually_Exclusive	MET, TP53	0/27
U2AF1	TP53	1	0	98	0	23	1	Mutually_Exclusive	TP53, U2AF1	0/24
KRAS	ERBB2	1	0	115	0	1	6	Mutually_Exclusive	ERBB2, KRAS	0/7
MAP2K1	ERBB2	1	0	120	0	1	1	Mutually_Exclusive	ERBB2, MAP2K1	0/2
MED12	ERBB2	1	0	115	0	1	6	Mutually_Exclusive	ERBB2, MED12	0/7
NF1	ERBB2	1	0	116	0	1	5	Mutually_Exclusive	ERBB2, NF1	0/6
MET	ERBB2	1	0	117	0	1	4	Mutually_Exclusive	ERBB2, MET	0/5
SETD2	ERBB2	1	0	116	0	1	5	Mutually_Exclusive	ERBB2, SETD2	0/6
U2AF1	ERBB2	1	0	120	0	1	1	Mutually_Exclusive	ERBB2, U2AF1	0/2
MAP2K1	KRAS	1	0	115	0	6	1	Mutually_Exclusive	KRAS, MAP2K1	0/7
MED12	KRAS	1	0	110	0	6	6	Mutually_Exclusive	KRAS, MED12	0/12
SETD2	KRAS	1	0	111	0	6	5	Mutually_Exclusive	KRAS, SETD2	0/11

U2AF1	KRAS	1	0	115	0	6	1	Mutually_Exclusive	KRAS, U2AF1	0/7
MED12	MAP2K1	1	0	115	0	1	6	Mutually_Exclusive	MAP2K1, MED12	0/7
NF1	MAP2K1	1	0	116	0	1	5	Mutually_Exclusive	MAP2K1, NF1	0/6
MET	MAP2K1	1	0	117	0	1	4	Mutually_Exclusive	MAP2K1, MET	0/5
SETD2	MAP2K1	1	0	116	0	1	5	Mutually_Exclusive	MAP2K1, SETD2	0/6
U2AF1	MAP2K1	1	0	120	0	1	1	Mutually_Exclusive	MAP2K1, U2AF1	0/2
NF1	MED12	1	0	111	0	6	5	Mutually_Exclusive	MED12, NF1	0/11
SETD2	MED12	1	0	111	0	6	5	Mutually_Exclusive	MED12, SETD2	0/11
U2AF1	MED12	1	0	115	0	6	1	Mutually_Exclusive	MED12, U2AF1	0/7
SETD2	NF1	1	0	112	0	5	5	Mutually_Exclusive	NF1, SETD2	0/10
U2AF1	NF1	1	0	116	0	5	1	Mutually_Exclusive	NF1, U2AF1	0/6
U2AF1	MET	1	0	117	0	4	1	Mutually_Exclusive	MET, U2AF1	0/5
U2AF1	SETD2	1	0	116	0	5	1	Mutually_Exclusive	SETD2, U2AF1	0/6

Table S12. Pathway Alteration Comparison between Radiologic Subtypes (Alteration Frequency > 0.01 were included).

Fisher's Exact Test (pGGN vs. HGGN)

Pathway	**pGGN_mut_num**	**pGGN_nomut_num**	**HGGN_mut_num**	**HGGN_nomut_num**	**total_mutfreq**	**pGGN_mutfreq**	**HGGN_mutfreq**	**mut_dif**	**p_value**	**q_value**
RTK_RAS	50	27	37	11	0.696	0.649351	0.770833	0.121483	0.167217	1
p53	6	71	3	45	0.072	0.077922	0.0625	0.015422	1	1
RNA_splicing	9	68	4	44	0.104	0.116883	0.083333	0.03355	0.764694	1
PI3K	5	72	3	45	0.064	0.064935	0.0625	0.002435	1	1
Cell_cycle	2	75	1	47	0.024	0.025974	0.020833	0.005141	1	1
Myc	3	74	2	46	0.04	0.038961	0.041667	0.002706	1	1
Wnt	0	77	1	47	0.008	0	0.020833	0.020833	0.384	1
Hippo	0	77	0	48	0	0	0	0	1	1
Notch	2	75	0	48	0.016	0.025974	0	0.025974	0.523097	1
TGFB	0	77	0	48	0	0	0	0	1	1

Fisher's Exact Test (pGGN vs. PSN)

Pathway	**pGGN_mut_num**	**pGGN_nomut_num**	**PSN_mut_num**	**PSN_nomut_num**	**total_mutfreq**	**pGGN_mutfreq**	**PSN_mutfreq**	**mut_dif**	**p_value**	**q_value**
RTK_RAS	50	27	93	29	0.718593	0.649351	0.762295	0.112944	0.105526	0.319813
p53	6	71	31	91	0.18593	0.077922	0.254098	0.176176	0.002397	**0.023971**
RNA_splicing	9	68	18	104	0.135678	0.116883	0.147541	0.030658	0.671835	0.678492
PI3K	5	72	11	111	0.080402	0.064935	0.090164	0.025229	0.601549	0.678492

Cell_cycle	2	75	12	110	0.070352	0.025974	0.098361	0.072387	0.084428	0.319813
Myc	3	74	3	119	0.030151	0.038961	0.02459	0.014371	0.678492	0.678492
Wnt	0	77	4	118	0.020101	0	0.032787	0.032787	0.159906	0.319813
Hippo	0	77	3	119	0.015075	0	0.02459	0.02459	0.284757	0.474595
Notch	2	75	0	122	0.01005	0.025974	0	0.025974	0.14852	0.319813
TGFB	0	77	2	120	0.01005	0	0.016393	0.016393	0.523171	0.678492

Fisher's Exact Test (HGGN vs. PSN)

Pathway	**HGGN_mut_num**	**HGGN_nomut_num**	**PSN_mut_num**	**PSN_nomut_num**	**total_mutfreq**	**HGGN_mutfreq**	**PSN_mutfreq**	**mut_dif**	**p_value**	**q_value**
RTK_RAS	37	11	93	29	0.764706	0.770833	0.762295	0.008538	1	1
p53	3	45	31	91	0.2	0.0625	0.254098	0.191598	0.004964	**0.049642**
RNA_splicing	4	44	18	104	0.129412	0.083333	0.147541	0.064208	0.318674	1
PI3K	3	45	11	111	0.082353	0.0625	0.090164	0.027664	0.759329	1
Cell_cycle	1	47	12	110	0.076471	0.020833	0.098361	0.077527	0.113279	0.566395
Myc	2	46	3	119	0.029412	0.041667	0.02459	0.017077	0.621893	1
Wnt	1	47	4	118	0.029412	0.020833	0.032787	0.011954	1	1
Hippo	0	48	3	119	0.017647	0	0.02459	0.02459	0.559584	1
Notch	0	48	0	122	0	0	0	0	1	1

TGFB	0	48	2	120	0.011765	0	0.016393	0.016393	1	1

Cochran-Armitage Trend Test

Pathway	pGGN_mut_num	pGGN_nomut_num	HGGN_mut_num	HGGN_nomut_num	PSN_mut_num	PSN_nomut_num	pGGN_mutfreq	HGGN_mutfreq	PSN_mutfreq	**p_value**
RTK_RAS	50	27	37	11	93	29	0.649351	0.770833	0.762295	0.09653
p53	6	71	3	45	31	91	0.077922	0.0625	0.254098	**0.0005**
RNA_splicing	9	68	4	44	18	104	0.116883	0.083333	0.147541	0.463839
PI3K	5	72	3	45	11	111	0.064935	0.0625	0.090164	0.490411
Cell_cycle	2	75	1	47	12	110	0.025974	0.020833	0.098361	**0.027606**
Myc	3	74	2	46	3	119	0.038961	0.041667	0.02459	0.551156
Wnt	0	77	1	47	4	118	0	0.020833	0.032787	0.112294
Hippo	0	77	0	48	3	119	0	0	0.02459	0.104903
Notch	2	75	0	48	0	122	0.025974	0	0	0.056139
TGFB	0	77	0	48	2	120	0	0	0.016393	0.186411

Table S13. Pathway Alteration Comparison between Radiologic Subtypes (WES Cohort).

Fisher's Exact Test (pGGN vs. HGGN)

Pathway	**pGGN_mut_num**	**pGGN_nomut_num**	**HGGN_mut_num**	**HGGN_nomut_num**	**total_mutfreq**	**pGGN_mutfreq**	**HGGN_mutfreq**	**mut_dif**	**p_value**	**q_value**
RTK_RAS	25	23	16	13	0.532468	0.520833	0.551724	0.030891	0.817945	0.817945
RNA_splicing	3	45	7	22	0.12987	0.0625	0.241379	0.178879	0.035441	0.141763
p53	3	45	5	24	0.103896	0.0625	0.172414	0.109914	0.144775	0.28955
PI3K	5	43	1	28	0.077922	0.104167	0.034483	0.069684	0.400241	0.533655

Fisher's Exact Test (pGGN vs. PSN)

Pathway	**pGGN_mut_num**	**pGGN_nomut_num**	**PSN_mut_num**	**PSN_nomut_num**	**total_mutfreq**	**pGGN_mutfreq**	**PSN_mutfreq**	**mut_dif**	**p_value**	**q_value**
RTK_RAS	25	23	37	11	0.645833	0.520833	0.770833	0.25	0.018261	**0.024348**
RNA_splicing	3	45	13	35	0.166667	0.0625	0.270833	0.208333	0.011886	**0.023771**
p53	3	45	13	35	0.166667	0.0625	0.270833	0.208333	0.011886	**0.023771**
PI3K	5	43	3	45	0.083333	0.104167	0.0625	0.041667	0.714471	0.714471

Fisher's Exact Test (HGGN vs. PSN)

Pathway	**HGGN_mut_num**	**HGGN_nomut_num**	**PSN_mut_num**	**PSN_nomut_num**	**total_mutfreq**	**HGGN_mutfreq**	**PSN_mutfreq**	**mut_dif**	**p_value**	**q_value**
RTK_RAS	16	13	37	11	0.688312	0.551724	0.770833	0.219109	0.074215	0.296862
RNA_splicing	7	22	13	35	0.25974	0.241379	0.270833	0.029454	1	1

p53	5	24	13	35	0.233766	0.172414	0.270833	0.09842	0.410237	0.820473
PI3K	1	28	3	45	0.051948	0.034483	0.0625	0.028017	1	1

Cochran-Armitage Trend Test

Pathway	pGGN_mut_num	pGGN_nomut_num	HGGN_mut_num	HGGN_nomut_num	PSN_mut_num	PSN_nomut_num	pGGN_mutfreq	HGGN_mutfreq	PSN_mutfreq	p_value
RTK_RAS	25	23	16	13	37	11	0.520833	0.551724	0.770833	**0.011456**
RNA_splicing	3	45	7	22	13	35	0.0625	0.241379	0.270833	**0.008439**
p53	3	45	5	24	13	35	0.0625	0.172414	0.270833	**0.006335**
PI3K	5	43	1	28	3	45	0.104167	0.034483	0.0625	0.429711

Table S14. Pathway Alteration Comparison between Radiologic Subtypes (IAC).

Fisher's Exact Test (pGGN vs. HGGN)

Pathway	pGGN_mut_num	pGGN_nomut_num	HGGN_mut_num	HGGN_nomut_num	total_mutfreq	pGGN_mutfreq	HGGN_mutfreq	mut_dif	p_value	q_value
RTK_RAS	22	9	25	6	0.75806452	0.70967742	0.80645161	0.09677419	0.55414549	1
p53	4	27	3	28	0.11290323	0.12903226	0.09677419	0.03225806	1	1
RNA_splicing	6	25	3	28	0.14516129	0.19354839	0.09677419	0.09677419	0.47292775	1
PI3K	2	29	2	29	0.06451613	0.06451613	0.06451613	0	1	1
Cell_cycle	1	30	1	30	0.03225806	0.03225806	0.03225806	0	1	1
Myc	2	29	1	30	0.0483871	0.06451613	0.03225806	0.03225806	1	1
Wnt	0	31	1	30	0.01612903	0	0.03225806	0.03225806	1	1
Hippo	0	31	0	31	0	0	0	0	1	1

Fisher's Exact Test (pGGN vs. PSN)

Pathway	pGGN_mut_num	pGGN_nomut_num	PSN_mut_num	PSN_nomut_num	total_mutfreq	pGGN_mutfreq	PSN_mutfreq	mut_dif	p_value	q_value
RTK_RAS	22	9	90	25	0.76712329	0.70967742	0.7826087	0.07293128	0.472834	0.77148103
p53	4	27	31	84	0.23972603	0.12903226	0.26956522	0.14053296	0.15370098	0.77148103
RNA_splicing	6	25	16	99	0.15068493	0.19354839	0.13913043	0.05441795	0.57112231	0.77148103
PI3K	2	29	10	105	0.08219178	0.06451613	0.08695652	0.02244039	1	1
Cell_cycle	1	30	11	104	0.08219178	0.03225806	0.09565217	0.06339411	0.46158636	0.77148103
Myc	2	29	2	113	0.02739726	0.06451613	0.0173913	0.04712482	0.19800114	0.77148103

Wnt	0	31	4	111	0.02739726	0	0.03478261	0.03478261	0.57861077	0.77148103
Hippo	0	31	3	112	0.02054795	0	0.02608696	0.02608696	1	1

Fisher's Exact Test (HGGN vs. PSN)

Pathway	**HGGN_mut_num**	**HGGN_nomut_num**	**PSN_mut_num**	**PSN_nomut_num**	**total_mutfreq**	**HGGN_mutfreq**	**PSN_mutfreq**	**mut_dif**	**p_value**	**q_value**
RTK_RAS	25	6	90	25	0.78767123	0.80645161	0.7826087	0.02384292	1	1
p53	3	28	31	84	0.23287671	0.09677419	0.26956522	0.17279102	0.05472575	0.43780602
RNA_splicing	3	28	16	99	0.13013699	0.09677419	0.13913043	0.04235624	0.76478113	1
PI3K	2	29	10	105	0.08219178	0.06451613	0.08695652	0.02244039	1	1
Cell_cycle	1	30	11	104	0.08219178	0.03225806	0.09565217	0.06339411	0.46158636	1
Myc	1	30	2	113	0.02054795	0.03225806	0.0173913	0.01486676	0.51404306	1
Wnt	1	30	4	111	0.03424658	0.03225806	0.03478261	0.00252454	1	1
Hippo	0	31	3	112	0.02054795	0	0.02608696	0.02608696	1	1

Cochran-Armitage Trend Test

Pathway	pGGN_mut_num	pGGN_nomut_num	HGGN_mut_num	HGGN_nomut_num	PSN_mut_num	PSN_nomut_num	pGGN_mutfreq	HGGN_mutfreq	PSN_mutfreq	**p_value**
RTK_RAS	22	9	25	6	90	25	0.70967742	0.80645161	0.7826087	0.48873015
p53	4	27	3	28	31	84	0.12903226	0.09677419	0.26956522	**0.03404256**
RNA_splicing	6	25	3	28	16	99	0.19354839	0.09677419	0.13913043	0.60332365

PI3K	2	29	2	29	10	105	0.06451613	0.06451613	0.08695652	0.6257861 1
Cell_cycle	1	30	1	30	11	104	0.03225806	0.03225806	0.09565217	0.15407118
Myc	2	29	1	30	2	113	0.06451613	0.03225806	0.0173913	0.16447568
Wnt	0	31	1	30	4	111	0	0.03225806	0.03478261	0.34045683
Hippo	0	31	0	31	3	112	0	0	0.02608696	0.23588791

Table S15. Co-occurrence and Mutual Exclusivity of Oncogenic Pathway in the Entire Cohort.

pathway1	**pathway2**	**pValue**	**oddsRatio**	**0/0**	**1/1**	**0/1**	**1/0**	**Event**	**pair**	**event_ratio**
PI3K	Myc	7.63E-05	25.79558	225	5	3	14	Co_Occurence	Myc, PI3K	5/17
Cell_cycle	PI3K	0.000298	10.98951	219	6	13	9	Co_Occurence	Cell_cycle, PI3K	6/22
Myc	Cell_cycle	0.008508	11.07481	227	3	12	5	Co_Occurence	Cell_cycle, Myc	3/17
RNA_splicing	RTK_RAS	0.017801	3.91345	64	28	152	3	Co_Occurence	RNA_splicing, RTK_RAS	28/155
Cell_cycle	p53	0.020257	3.852358	198	6	34	9	Co_Occurence	Cell_cycle, p53	6/43
RTK_RAS	TGFB	0.072776	0	65	0	2	180	Mutually_Exclusive	RTK_RAS, TGFB	0/182
Myc	RTK_RAS	0.112083	Inf	67	8	172	0	Co_Occurence	Myc, RTK_RAS	8/172
PI3K	Notch	0.148218	12.30189	227	1	1	18	Co_Occurence	Notch, PI3K	1/19
Myc	RNA_splicing	0.264468	2.402286	210	2	29	6	Co_Occurence	Myc, RNA_splicing	2/35
RTK_RAS	PI3K	0.295941	2.076047	64	16	3	164	Co_Occurence	PI3K, RTK_RAS	16/167
RNA_splicing	p53	0.301813	1.613885	183	7	33	24	Co_Occurence	p53, RNA_splicing	7/57
PI3K	Wnt	0.332109	3.088759	224	1	4	18	Co_Occurence	PI3K, Wnt	1/22
RNA_splicing	Hippo	0.332413	3.538596	214	1	2	30	Co_Occurence	Hippo, RNA_splicing	1/32
Myc	p53	0.360773	0	199	0	40	8	Mutually_Exclusive	Myc, p53	0/48
RTK_RAS	Cell_cycle	0.367573	2.5223	65	13	2	167	Co_Occurence	Cell_cycle, RTK_RAS	13/169
p53	Hippo	0.41279	2.614574	205	1	2	39	Co_Occurence	Hippo, p53	1/41
RTK_RAS	Notch	0.469734	0.370464	66	1	1	179	Mutually_Exclusive	Notch, RTK_RAS	1/180
Hippo	RTK_RAS	0.564966	Inf	67	3	177	0	Co_Occurence	Hippo, RTK_RAS	3/177
Wnt	p53	0.589868	1.299773	203	1	39	4	Co_Occurence	p53, Wnt	1/43
Cell_cycle	RNA_splicing	0.701108	0.48207	202	1	30	14	Mutually_Exclusive	Cell_cycle, RNA_splicing	1/44

RTK_RAS	p53	1	0.977794	56	29	11	151	Mutually_Exclusive	p53, RTK_RAS	29/162
Notch	p53	1	0	205	0	40	2	Mutually_Exclusive	Notch, p53	0/42
TGFB	p53	1	0	205	0	40	2	Mutually_Exclusive	p53, TGFB	0/42
Hippo	PI3K	1	0	225	0	19	3	Mutually_Exclusive	Hippo, PI3K	0/22
TGFB	PI3K	1	0	226	0	19	2	Mutually_Exclusive	PI3K, TGFB	0/21
Wnt	Myc	1	0	234	0	8	5	Mutually_Exclusive	Myc, Wnt	0/13
Cell_cycle	Wnt	1	0	227	0	5	15	Mutually_Exclusive	Cell_cycle, Wnt	0/20
Hippo	Wnt	1	0	239	0	5	3	Mutually_Exclusive	Hippo, Wnt	0/8
Notch	Hippo	1	0	242	0	3	2	Mutually_Exclusive	Hippo, Notch	0/5
TGFB	Hippo	1	0	242	0	3	2	Mutually_Exclusive	Hippo, TGFB	0/5
Wnt	RTK_RAS	1	1.497834	66	4	176	1	Co_Occurence	RTK_RAS, Wnt	4/177
PI3K	p53	1	0.968024	191	3	37	16	Mutually_Exclusive	p53, PI3K	3/53
PI3K	RNA_splicing	1	0.807956	199	2	29	17	Mutually_Exclusive	PI3K, RNA_splicing	2/46
Wnt	RNA_splicing	1	0	211	0	31	5	Mutually_Exclusive	RNA_splicing, Wnt	0/36
Notch	RNA_splicing	1	0	214	0	31	2	Mutually_Exclusive	Notch, RNA_splicing	0/33
TGFB	RNA_splicing	1	0	214	0	31	2	Mutually_Exclusive	RNA_splicing, TGFB	0/33
Hippo	Cell_cycle	1	0	229	0	15	3	Mutually_Exclusive	Cell_cycle, Hippo	0/18
Notch	Cell_cycle	1	0	230	0	15	2	Mutually_Exclusive	Cell_cycle, Notch	0/17
TGFB	Cell_cycle	1	0	230	0	15	2	Mutually_Exclusive	Cell_cycle, TGFB	0/17
Hippo	Myc	1	0	236	0	8	3	Mutually_Exclusive	Hippo, Myc	0/11
Notch	Myc	1	0	237	0	8	2	Mutually_Exclusive	Myc, Notch	0/10
TGFB	Myc	1	0	237	0	8	2	Mutually_Exclusive	Myc, TGFB	0/10

Notch	Wnt	1	0	240	0	5	2	Mutually_Exclusive	Notch, Wnt	0/7
TGFB	Wnt	1	0	240	0	5	2	Mutually_Exclusive	TGFB, Wnt	0/7
TGFB	Notch	1	0	243	0	2	2	Mutually_Exclusive	Notch, TGFB	0/4

Table S16. Co-occurrence and Mutual Exclusivity of Oncogenic Pathway in pGGN Cohort.

pathway1	**pathway2**	**pValue**	**oddsRatio**	**0/0**	**1/1**	**0/1**	**1/0**	**Event**	**pair**	**event_ratio**
Cell_cycle	PI3K	0.003418	Inf	72	2	3	0	Co_Occurence	Cell_cycle, PI3K	2/3
Myc	Cell_cycle	0.076897	30.00147	73	1	1	2	Co_Occurence	Cell_cycle, Myc	1/3
Notch	PI3K	0.126452	15.99265	71	1	4	1	Co_Occurence	Notch, PI3K	1/5
RNA_splicing	p53	0.142658	4.432676	64	2	4	7	Co_Occurence	p53, RNA_splicing	2/11
RNA_splicing	RTK_RAS	0.14881	4.874129	26	8	42	1	Co_Occurence	RNA_splicing, RTK_RAS	8/43
PI3K	Myc	0.184689	8.213455	70	1	2	4	Co_Occurence	Myc, PI3K	1/6
Myc	RNA_splicing	0.314887	4.007489	66	1	8	2	Co_Occurence	Myc, RNA_splicing	1/10
Cell_cycle	RTK_RAS	0.538619	Inf	27	2	48	0	Co_Occurence	Cell_cycle, RTK_RAS	2/48
Myc	RTK_RAS	0.547847	Inf	27	3	47	0	Co_Occurence	Myc, RTK_RAS	3/47
PI3K	RNA_splicing	1	0	63	0	9	5	Mutually_Exclusive	PI3K, RNA_splicing	0/14
Myc	Notch	1	0	72	0	2	3	Mutually_Exclusive	Myc, Notch	0/5
p53	RTK_RAS	1	1.085804	25	4	46	2	Co_Occurence	p53, RTK_RAS	4/48
PI3K	RTK_RAS	1	0.800296	25	3	47	2	Mutually_Exclusive	PI3K, RTK_RAS	3/49
Wnt	RTK_RAS	1	0	27	0	50	0	Mutually_Exclusive	RTK_RAS, Wnt	0/50
Hippo	RTK_RAS	1	0	27	0	50	0	Mutually_Exclusive	Hippo, RTK_RAS	0/50
Notch	RTK_RAS	1	0.535266	26	1	49	1	Mutually_Exclusive	Notch, RTK_RAS	1/50
TGFB	RTK_RAS	1	0	27	0	50	0	Mutually_Exclusive	RTK_RAS, TGFB	0/50
PI3K	p53	1	0	66	0	6	5	Mutually_Exclusive	p53, PI3K	0/11
Cell_cycle	p53	1	0	69	0	6	2	Mutually_Exclusive	Cell_cycle, p53	0/8
Myc	p53	1	0	68	0	6	3	Mutually_Exclusive	Myc, p53	0/9

Wnt	p53	1	0	71	0	6	0	Mutually_Exclusive	p53, Wnt	0/6
Hippo	p53	1	0	71	0	6	0	Mutually_Exclusive	Hippo, p53	0/6
Notch	p53	1	0	69	0	6	2	Mutually_Exclusive	Notch, p53	0/8
TGFB	p53	1	0	71	0	6	0	Mutually_Exclusive	p53, TGFB	0/6
Cell_cycle	RNA_splicing	1	0	66	0	9	2	Mutually_Exclusive	Cell_cycle, RNA_splicing	0/11
Wnt	RNA_splicing	1	0	68	0	9	0	Mutually_Exclusive	RNA_splicing, Wnt	0/9
Hippo	RNA_splicing	1	0	68	0	9	0	Mutually_Exclusive	Hippo, RNA_splicing	0/9
Notch	RNA_splicing	1	0	66	0	9	2	Mutually_Exclusive	Notch, RNA_splicing	0/11
TGFB	RNA_splicing	1	0	68	0	9	0	Mutually_Exclusive	RNA_splicing, TGFB	0/9
Wnt	PI3K	1	0	72	0	5	0	Mutually_Exclusive	PI3K, Wnt	0/5
Hippo	PI3K	1	0	72	0	5	0	Mutually_Exclusive	Hippo, PI3K	0/5
TGFB	PI3K	1	0	72	0	5	0	Mutually_Exclusive	PI3K, TGFB	0/5
Wnt	Cell_cycle	1	0	75	0	2	0	Mutually_Exclusive	Cell_cycle, Wnt	0/2
Hippo	Cell_cycle	1	0	75	0	2	0	Mutually_Exclusive	Cell_cycle, Hippo	0/2
Notch	Cell_cycle	1	0	73	0	2	2	Mutually_Exclusive	Cell_cycle, Notch	0/4
TGFB	Cell_cycle	1	0	75	0	2	0	Mutually_Exclusive	Cell_cycle, TGFB	0/2
Wnt	Myc	1	0	74	0	3	0	Mutually_Exclusive	Myc, Wnt	0/3
Hippo	Myc	1	0	74	0	3	0	Mutually_Exclusive	Hippo, Myc	0/3
TGFB	Myc	1	0	74	0	3	0	Mutually_Exclusive	Myc, TGFB	0/3
Hippo	Wnt	1	0	77	0	0	0	Mutually_Exclusive	Hippo, Wnt	0/0
Notch	Wnt	1	0	75	0	0	2	Mutually_Exclusive	Notch, Wnt	0/2
TGFB	Wnt	1	0	77	0	0	0	Mutually_Exclusive	TGFB, Wnt	0/0

Notch	Hippo	1	0	75	0	0	2	Mutually_Exclusive	Hippo, Notch	0/2
TGFB	Hippo	1	0	77	0	0	0	Mutually_Exclusive	Hippo, TGFB	0/0
TGFB	Notch	1	0	75	0	2	0	Mutually_Exclusive	Notch, TGFB	0/2

Table S17. Co-occurrence and Mutual Exclusivity of Oncogenic Pathway in HGGN Cohort.

pathway1	**pathway2**	**pValue**	**oddsRatio**	**0/0**	**1/1**	**0/1**	**1/0**	**Event**	**pair**	**event_ratio**
PI3K	Myc	0.00266	Inf	45	2	0	1	Co_Occurence	Myc, PI3K	2/1
p53	RTK_RAS	0.550763	0.579013	10	2	35	1	Mutually_Exclusive	p53, RTK_RAS	2/36
RNA_splicing	RTK_RAS	0.560746	Inf	11	4	33	0	Co_Occurence	RNA_splicing, RTK_RAS	4/33
p53	Myc	1	0	43	0	2	3	Mutually_Exclusive	Myc, p53	0/5
PI3K	RTK_RAS	1	Inf	11	3	34	0	Co_Occurence	PI3K, RTK_RAS	3/34
Cell_cycle	RTK_RAS	1	Inf	11	1	36	0	Co_Occurence	Cell_cycle, RTK_RAS	1/36
Myc	RTK_RAS	1	Inf	11	2	35	0	Co_Occurence	Myc, RTK_RAS	2/35
Wnt	RTK_RAS	1	Inf	11	1	36	0	Co_Occurence	RTK_RAS, Wnt	1/36
Hippo	RTK_RAS	1	0	11	0	37	0	Mutually_Exclusive	Hippo, RTK_RAS	0/37
Notch	RTK_RAS	1	0	11	0	37	0	Mutually_Exclusive	Notch, RTK_RAS	0/37
TGFB	RTK_RAS	1	0	11	0	37	0	Mutually_Exclusive	RTK_RAS, TGFB	0/37
RNA_splicing	p53	1	0	41	0	3	4	Mutually_Exclusive	p53, RNA_splicing	0/7
PI3K	p53	1	0	42	0	3	3	Mutually_Exclusive	p53, PI3K	0/6
Cell_cycle	p53	1	0	44	0	3	1	Mutually_Exclusive	Cell_cycle, p53	0/4
Wnt	p53	1	0	44	0	3	1	Mutually_Exclusive	p53, Wnt	0/4
Hippo	p53	1	0	45	0	3	0	Mutually_Exclusive	Hippo, p53	0/3
Notch	p53	1	0	45	0	3	0	Mutually_Exclusive	Notch, p53	0/3
TGFB	p53	1	0	45	0	3	0	Mutually_Exclusive	p53, TGFB	0/3
PI3K	RNA_splicing	1	0	41	0	4	3	Mutually_Exclusive	PI3K, RNA_splicing	0/7
Cell_cycle	RNA_splicing	1	0	43	0	4	1	Mutually_Exclusive	Cell_cycle, RNA_splicing	0/5

Myc	RNA_splicing	1	0	42	0	4	2	Mutually_Exclusive	Myc, RNA_splicing	0/6
Wnt	RNA_splicing	1	0	43	0	4	1	Mutually_Exclusive	RNA_splicing, Wnt	0/5
Hippo	RNA_splicing	1	0	44	0	4	0	Mutually_Exclusive	Hippo, RNA_splicing	0/4
Notch	RNA_splicing	1	0	44	0	4	0	Mutually_Exclusive	Notch, RNA_splicing	0/4
TGFB	RNA_splicing	1	0	44	0	4	0	Mutually_Exclusive	RNA_splicing, TGFB	0/4
Cell_cycle	PI3K	1	0	44	0	3	1	Mutually_Exclusive	Cell_cycle, PI3K	0/4
Wnt	PI3K	1	0	44	0	3	1	Mutually_Exclusive	PI3K, Wnt	0/4
Hippo	PI3K	1	0	45	0	3	0	Mutually_Exclusive	Hippo, PI3K	0/3
Notch	PI3K	1	0	45	0	3	0	Mutually_Exclusive	Notch, PI3K	0/3
TGFB	PI3K	1	0	45	0	3	0	Mutually_Exclusive	PI3K, TGFB	0/3
Myc	Cell_cycle	1	0	45	0	1	2	Mutually_Exclusive	Cell_cycle, Myc	0/3
Wnt	Cell_cycle	1	0	46	0	1	1	Mutually_Exclusive	Cell_cycle, Wnt	0/2
Hippo	Cell_cycle	1	0	47	0	1	0	Mutually_Exclusive	Cell_cycle, Hippo	0/1
Notch	Cell_cycle	1	0	47	0	1	0	Mutually_Exclusive	Cell_cycle, Notch	0/1
TGFB	Cell_cycle	1	0	47	0	1	0	Mutually_Exclusive	Cell_cycle, TGFB	0/1
Wnt	Myc	1	0	45	0	2	1	Mutually_Exclusive	Myc, Wnt	0/3
Hippo	Myc	1	0	46	0	2	0	Mutually_Exclusive	Hippo, Myc	0/2
Notch	Myc	1	0	46	0	2	0	Mutually_Exclusive	Myc, Notch	0/2
TGFB	Myc	1	0	46	0	2	0	Mutually_Exclusive	Myc, TGFB	0/2
Hippo	Wnt	1	0	47	0	1	0	Mutually_Exclusive	Hippo, Wnt	0/1
Notch	Wnt	1	0	47	0	1	0	Mutually_Exclusive	Notch, Wnt	0/1
TGFB	Wnt	1	0	47	0	1	0	Mutually_Exclusive	TGFB, Wnt	0/1

Notch	Hippo	1	0	48	0	0	0	Mutually_Exclusive	Hippo, Notch	0/0
TGFB	Hippo	1	0	48	0	0	0	Mutually_Exclusive	Hippo, TGFB	0/0
TGFB	Notch	1	0	48	0	0	0	Mutually_Exclusive	Notch, TGFB	0/0

Table S18. Co-occurrence and Mutual Exclusivity of Oncogenic Pathway in PSN Cohort.

pathway1	**pathway2**	**pValue**	**oddsRatio**	**0/0**	**1/1**	**0/1**	**1/0**	**Event**	**pair**	**event_ratio**
Cell_cycle	PI3K	0.012518	7.144426	103	4	7	8	Co_Occurence	Cell_cycle, PI3K	4/15
PI3K	Myc	0.021237	22.89258	110	2	1	9	Co_Occurence	Myc, PI3K	2/10
Myc	Cell_cycle	0.025335	20.55864	109	2	10	1	Co_Occurence	Cell_cycle, Myc	2/11
RTK_RAS	TGFB	0.055006	0	27	0	2	93	Mutually_Exclusive	RTK_RAS, TGFB	0/95
Cell_cycle	p53	0.073364	3.358547	85	6	25	6	Co_Occurence	Cell_cycle, p53	6/31
RTK_RAS	RNA_splicing	0.236231	2.786155	27	16	2	77	Co_Occurence	RNA_splicing, RTK_RAS	16/79
Wnt	PI3K	0.318144	3.540184	108	1	10	3	Co_Occurence	PI3K, Wnt	1/13
RNA_splicing	Myc	0.3832	2.962658	102	1	2	17	Co_Occurence	Myc, RNA_splicing	1/19
RNA_splicing	Hippo	0.3832	2.962658	102	1	2	17	Co_Occurence	Hippo, RNA_splicing	1/19
PI3K	RTK_RAS	0.456533	3.348449	28	10	83	1	Co_Occurence	PI3K, RTK_RAS	10/84
Myc	p53	0.570028	0	88	0	31	3	Mutually_Exclusive	Myc, p53	0/34
RNA_splicing	PI3K	0.665199	1.316203	95	2	9	16	Co_Occurence	PI3K, RNA_splicing	2/25
RTK_RAS	Cell_cycle	0.72924	1.62072	27	10	2	83	Co_Occurence	Cell_cycle, RTK_RAS	10/85
p53	RNA_splicing	0.775571	1.152441	78	5	13	26	Co_Occurence	p53, RNA_splicing	5/39
p53	RTK_RAS	0.808558	0.863578	21	23	70	8	Mutually_Exclusive	p53, RTK_RAS	23/78
TGFB	p53	1	0	89	0	31	2	Mutually_Exclusive	p53, TGFB	0/33
Hippo	PI3K	1	0	108	0	11	3	Mutually_Exclusive	Hippo, PI3K	0/14
Wnt	TGFB	1	0	116	0	2	4	Mutually_Exclusive	TGFB, Wnt	0/6
Myc	RTK_RAS	1	Inf	29	3	90	0	Co_Occurence	Myc, RTK_RAS	3/90
Wnt	RTK_RAS	1	0.933864	28	3	90	1	Mutually_Exclusive	RTK_RAS, Wnt	3/91

Hippo	RTK_RAS	1	Inf	29	3	90	0	Co_Occurence	Hippo, RTK_RAS	3/90
Notch	RTK_RAS	1	0	29	0	93	0	Mutually_Exclusive	Notch, RTK_RAS	0/93
PI3K	p53	1	1.110614	83	3	28	8	Co_Occurence	p53, PI3K	3/36
Wnt	p53	1	0.977948	88	1	30	3	Mutually_Exclusive	p53, Wnt	1/33
Hippo	p53	1	1.478124	89	1	30	2	Co_Occurence	Hippo, p53	1/32
Notch	p53	1	0	91	0	31	0	Mutually_Exclusive	Notch, p53	0/31
Cell_cycle	RNA_splicing	1	0.499658	93	1	17	11	Mutually_Exclusive	Cell_cycle, RNA_splicing	1/28
Wnt	RNA_splicing	1	0	100	0	18	4	Mutually_Exclusive	RNA_splicing, Wnt	0/22
Notch	RNA_splicing	1	0	104	0	18	0	Mutually_Exclusive	Notch, RNA_splicing	0/18
TGFB	RNA_splicing	1	0	102	0	18	2	Mutually_Exclusive	RNA_splicing, TGFB	0/20
Notch	PI3K	1	0	111	0	11	0	Mutually_Exclusive	Notch, PI3K	0/11
TGFB	PI3K	1	0	109	0	11	2	Mutually_Exclusive	PI3K, TGFB	0/13
Wnt	Cell_cycle	1	0	106	0	12	4	Mutually_Exclusive	Cell_cycle, Wnt	0/16
Hippo	Cell_cycle	1	0	107	0	12	3	Mutually_Exclusive	Cell_cycle, Hippo	0/15
Notch	Cell_cycle	1	0	110	0	12	0	Mutually_Exclusive	Cell_cycle, Notch	0/12
TGFB	Cell_cycle	1	0	108	0	12	2	Mutually_Exclusive	Cell_cycle, TGFB	0/14
Wnt	Myc	1	0	115	0	3	4	Mutually_Exclusive	Myc, Wnt	0/7
Hippo	Myc	1	0	116	0	3	3	Mutually_Exclusive	Hippo, Myc	0/6
Notch	Myc	1	0	119	0	3	0	Mutually_Exclusive	Myc, Notch	0/3
TGFB	Myc	1	0	117	0	3	2	Mutually_Exclusive	Myc, TGFB	0/5
Hippo	Wnt	1	0	115	0	4	3	Mutually_Exclusive	Hippo, Wnt	0/7
Notch	Wnt	1	0	118	0	4	0	Mutually_Exclusive	Notch, Wnt	0/4

Notch	Hippo	1	0	119	0	3	0	Mutually_Exclusive	Hippo, Notch	0/3
TGFB	Hippo	1	0	117	0	3	2	Mutually_Exclusive	Hippo, TGFB	0/5
TGFB	Notch	1	0	120	0	0	2	Mutually_Exclusive	Notch, TGFB	0/2

Table S19. Mutational Signature (WES Cohort).

Mutation Type	Denovo S1	Denovo S2	Denovo S3
A[C>A]A	0.00844882	0.01946685	0.00929192
A[C>A]C	0.01058873	0.02122696	0.00821073
A[C>A]G	0.00184669	0.0215169	1.0589E-11
A[C>A]T	2.716E-19	0.01842074	0.00414456
C[C>A]A	3.449E-11	0.05122111	0.02365877
C[C>A]C	0.01045541	0.06708672	3.37E-19
C[C>A]G	2.716E-19	0.04869143	1.1935E-10
C[C>A]T	1.5885E-10	0.05732029	3.37E-19
G[C>A]A	0.0190271	0.02630604	0.00080165
G[C>A]C	0.00407225	0.0457637	0.00592003
G[C>A]G	0.00537509	0.01982475	0.00741142
G[C>A]T	0.017336	0.01516709	3.3332E-14
T[C>A]A	0.01891275	0.02226011	3.37E-19
T[C>A]C	0.01631495	0.04174828	0.00958281
T[C>A]G	0.00627723	0.01445268	0.00518635
T[C>A]T	0.02507557	0.02177685	0.00890603
A[C>G]A	2.716E-19	0.00545611	0.01501579
A[C>G]C	0.01163693	0.00014119	3.37E-19
A[C>G]G	2.716E-19	0.00173828	0.00961364
A[C>G]T	0.00856425	0.00140933	0.00186256
C[C>G]A	0.00523586	0.00906073	0.00657922
C[C>G]C	0.01169264	0.00277129	0.0038031
C[C>G]G	0.00850836	0.00687692	1.3772E-18
C[C>G]T	0.01323547	0.00616104	0.01131757
G[C>G]A	2.716E-19	0.00724006	0.00152769
G[C>G]C	4.1579E-13	0.00909036	0.00966213
G[C>G]G	0.00408743	0.00755287	0.00114838
G[C>G]T	0.00719203	0.00888754	0.00790054
T[C>G]A	0.01776683	0.00486097	0.00797798
T[C>G]C	0.00972665	0.00898891	0.01686515
T[C>G]G	0.00159686	0.00420948	0.00585366
T[C>G]T	0.01459438	0.00859953	0.02693444
A[C>T]A	0.0141157	0.00431551	0.01134806
A[C>T]C	0.01771037	0.00547925	0.01212854
A[C>T]G	0.07405467	3.8591E-16	2.3578E-10
A[C>T]T	0.00801849	0.00372638	0.00962502
C[C>T]A	0.00656859	0.01398342	0.05069011
C[C>T]C	0.01686089	0.01491764	0.03759897
C[C>T]G	0.06407284	0.01414436	0.02044592
C[C>T]T	0.03025947	0.01903944	0.0143036
G[C>T]A	0.03960585	0.0088074	2.4409E-13
G[C>T]C	0.02899051	0.01515088	0.02726619

G[C>T]G	0.05511271	0.01476673	0.04541827
G[C>T]T	0.02137418	0.00318731	0.03084419
T[C>T]A	0.0470116	0.00421427	0.02918832
T[C>T]C	0.02293701	0.01091017	0.042376
T[C>T]G	0.0566332	4.6588E-11	0.01869968
T[C>T]T	0.02618992	0.00676552	0.02849134
A[T>A]A	0.00299552	0.00392378	3.6104E-13
A[T>A]C	0.01341123	0.00388284	3.37E-19
A[T>A]G	0.0056275	0.01337879	0.00802115
A[T>A]T	0.00693047	0.00153862	0.00417338
C[T>A]A	0.007606	0.01735382	3.37E-19
C[T>A]C	2.716E-19	0.01270837	0.00975021
C[T>A]G	2.716E-19	0.0412509	0.01496448
C[T>A]T	0.00386995	0.01262914	0.00606077
G[T>A]A	0.00342073	0.00767632	0.00472554
G[T>A]C	0.00209547	0.01254846	3.37E-19
G[T>A]G	0.00396911	0.02108529	3.37E-19
G[T>A]T	0.00587019	5.8359E-10	4.5774E-12
T[T>A]A	0.00235987	0.00628285	0.00107134
T[T>A]C	0.0036265	0.00356112	0.00419744
T[T>A]G	5.0702E-17	0.01205714	0.00368671
T[T>A]T	2.716E-19	0.00223629	0.00635388
A[T>C]A	2.716E-19	0.00815518	0.03713226
A[T>C]C	0.00231934	0.00245345	0.01890427
A[T>C]G	8.7292E-07	0.00390926	0.04044552
A[T>C]T	0.00973085	0.00209677	0.03122011
C[T>C]A	2.716E-19	0.00573766	0.0099602
C[T>C]C	0.00456378	0.00379401	0.01134779
C[T>C]G	0.01721226	0.0137966	0.01457506
C[T>C]T	0.00904369	6.2698E-18	0.01828664
G[T>C]A	0.00870107	0.00048884	0.00809356
G[T>C]C	0.01806212	3.3476E-12	3.0852E-11
G[T>C]G	0.00838167	0.00928707	0.00838681
G[T>C]T	0.0099438	0.00647772	0.00845367
T[T>C]A	0.00495884	0.00238956	0.00416371
T[T>C]C	0.00543239	9.5927E-18	0.0209969
T[T>C]G	2.716E-19	0.00437761	0.00874432
T[T>C]T	0.00939367	2.936E-19	0.00487944
A[T>G]A	0.0076764	3.7598E-12	4.862E-11
A[T>G]C	9.6817E-12	2.936E-19	0.00745784
A[T>G]G	0.00149979	0.00138124	0.00707653
A[T>G]T	0.00451553	1.2218E-12	2.4834E-10
C[T>G]A	2.716E-19	0.00126421	0.0013213
C[T>G]C	0.0071664	0.00272902	0.00183172

C[T>G]G	0.0032099	0.0025394	0.03849015
C[T>G]T	0.00238831	0.00517183	0.00835264
G[T>G]A	9.4346E-12	2.936E-19	0.0047459
G[T>G]C	0.00136618	0.00121697	1.2777E-10
G[T>G]G	0.00472902	0.00094129	3.37E-19
G[T>G]T	2.4499E-11	2.936E-19	0.00813583
T[T>G]A	4.5747E-10	0.00108086	0.00694687
T[T>G]C	2.268E-11	2.936E-19	0.01084777
T[T>G]G	1.6891E-13	0.00389431	0.00859796
T[T>G]T	0.01083727	3.7835E-12	2.5454E-11