

**Supplementary Table 2 – Frequency of selected genes in SQ-MAP vs. TCGA**

	SQ-MAP (n=74)	TCGA (n=178)	p (Fisher's exact test)	p (adjusted for multiple testing)
EP300	17.6%	4.5%	0.0017	0.43
ARID1A	20.3%	6.7%	0.003	0.76
NFKB1	9.5%	1.1%	0.003	0.81
DDR2	8.1%	1.1%	0.009	1
AKT1	6.8%	0.6%	0.009	1
SMO	6.8%	0.6%	0.009	1
TET2	9.5%	2.3%	0.016	1
RET	8.1%	1.7%	0.021	1
EPHA10	10.8%	2.8%	0.023	1
DIS3	4.0%	0.00%	0.025	1
MITF	4.0%	0.00%	0.025	1
REL	4.0%	0.00%	0.025	1
LGR6	5.4%	0.6%	0.027	1
TMPRSS2	5.4%	0.6%	0.027	1
CBLB	10.8%	3.9%	0.045	1
FLT4	9.5%	2.8%	0.04	1
NF1	21.6%	11.2%	0.047	1

**Supplementary Table 3 – Clinical characteristics of patients with resected brain metastases**

<b>ID</b>	<b>Age</b>	<b>Sex</b>	<b>Race</b>	<b>Smoking status</b>	<b>Pack-years</b>	<b>Treatment</b>
PP1	51	Female	White	Former	10	cisplatin + docetaxel -> cisplatin + gemcitabine -> sequential RT; gemcitabine; nab-paclitaxel
PP2	88	Male	White	Former	50	carboplatin + paclitaxel
PP3	62	Female	White	Current	33	cisplatin + etoposide + concurrent RT
PP4	66	Female	White	Former	20	cisplatin + gemcitabine
PP5	67	Female	White	Former	50	carboplatin + paclitaxel + concurrent RT
PP6	77	Male	White	Current	53	carboplatin + paclitaxel

**Supplementary Table 4 – Genes exhibiting clonal evolution from primary lung tumors and matched brain metastases. Data from PP1 and PP4 are shown.**

<b>Subclonal in primary lung, clonal in brain metastasis</b>	
<b>PP1</b>	<b>PP4</b>
PCDHB6	MEI1
PCDHGA10	UNC45B
ANK2	SLC5A7
NUDT6	PCDH18
	CTBP1
	HTR2A
	PCDHGB2
	SCARA5
	PIWIL3
	C2ord53
	RNF144A
	PCDHGA4
	MORF4
	METTL4
	UBE4A
	C4orf37
	PSMD8
	PGK2
	KIAA1429

**Supplementary Table 5 – List of 279 oncogenes and tumor suppressors covered by the Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT) assay.**

ABL1	ABL2	AKT1	AKT2	AKT3	ALK	ALOX12B	APC	AR
ARAF	ARHGAP26	ARID1A	ARID2	ASXL1	ATM	ATRX	AURKA	BAP1
BCL2L1	BCL2L11	BCL6	BCOR	BIRC2	BRAF	BRCA1	BRCA2	BUB1B
CARD11	CBL	CBLB	CBLC	CCND1	CCNE1	CD79B	CDC42EP2	CDC73
CDH1	CDH11	CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN2A	CDKN2B
CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CRLF2	CSF1R
CTNNB1	CYLD	DAXX	DDR2	DICER1	DIS3	DNMT1	DNMT3A	DNMT3B
E2F3	EGFR	EIF4EBP1	EP300	EPHA10	EPHA2	EPHA3	EPHA4	EPHA5
EPHA6	EPHA7	EPHA8	EPHB1	EPHB2	EPHB3	EPHB4	EPHB6	ERBB2
ERBB3	ERBB4	ERG	ESR1	ETV1	ETV6	EZH2	FAM123B	FAM46C
FAS	FAT1	FBXO11	FBXW7	FGFR1	FGFR2	FGFR3	FGFR4	FH
FLCN	FLT1	FLT3	FLT4	FOXL2	FUBP1	GATA1	GATA2	GATA3
GLI1	GLI3	GNA11	GNAQ	GNAS	GOLPH3	GRIN2A	GRM3	GSK3B
HDAC2	HIF1A	HMGA2	HNF1A	HRAS	HSP90AA1	IDH1	IDH2	IGF1R
IGFBP7	IKBKE	IKZF1	IL7R	INPP4A	INPP4B	INSR	IRS1	IRS2
JAK1	JAK2	JAK3	JUN	KCNJ5	KDM5C	KDM6A	KDR	KEAP1
KIT	KLF6	KRAS	LDHA	LGR6	LMO1	MAGI2	MAP2K1	MAP2K2
MAP2K4	MAP3K1	MAP3K8	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MET	MITF	MLH1	MLL	MLL2	MLL3	MLST8	MPL	MSH2
MSH6	MTOR	MYB	MYC	MYCL1	MYCN	MYD88	NCOA2	NF1
NF2	NFE2L2	NFKB1	NFKB2	NKX2-1	NOTCH1	NOTCH2	NOTCH3	NOTCH4
NPM1	NRAS	NTRK1	NTRK2	NTRK3	PAK7	PALB2	PARK2	PARP1
PAX5	PBRM1	PDGFRA	PDGFRB	PHOX2B	PIK3C2G	PIK3CA	PIK3CB	PIK3CD
PIK3CG	PIK3R1	PIK3R2	PIK3R3	PKM2	PLK2	PNRC1	PPP2R1A	PRDM1
PREX2	PRKAA2	PRKAR1A	PRKCI	PTCH1	PTEN	PTPN11	PTPRD	PTPRS
PTPRT	RAF1	RARA	RB1	REL	RET	RICTOR	RNF43	ROR2

**Supplementary Table 6**– Computational estimates of tumor purity (fractional) from whole-exome sequencing data for the paired lung primary and brain metastasis tumor samples compared to pathological evaluation of tumor purity in the same samples.

<b>Sample</b>	<b>Computational estimate</b>	<b>Pathology estimate</b>
PP1 brain	0.83	0.90
PP1 lung	0.70	0.80
PP3 brain	0.73	0.70
PP5 brain	0.74	0.60
PP4 brain	0.52	0.60
PP4 lung	0.30	0.50
PP2 brain	0.84	0.80
PP2 lung	0.41	0.40