previously [6,7], we also found mutations in the *CREBBP* (2 cases), *EP300* (2 cases), Ephrin family (19 cases in 10 genes), and FLT family (7 cases in 3 genes) genes with low frequencies (<10%). Therefore, it is absolutely necessary to analyze a larger number of SCLCs to define the prevalence and clinical significance of their mutations. However, it is difficult to collect SCLC samples for molecular analysis, the present results will be highly informative to further define genes targetable for therapy of SCLC patients.

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Honoraria: Ryo Nishikawa, EISAI; Rui Yamaguchi and Seiya Imoto; Fujifilum

Consultant or Advisory Role: Ryo Nishikawa, Roche

Speaker's Bureau: Ryo Nishikawa, Chugai

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AUTHOR CONTRIBUTIONS

Conception and design: Reika Iwakawa, Takashi Kohno, Jun Yokota

Collection and assembly of data: Reika Iwakawa, Yasushi Totoki, Tatsuhiko Shibata, Katsuya Tsuchihara, Sachiyo Mimaki, Koji Tsuta, Yoshitaka Narita, Ryo Nishikawa, Masayuki Noguchi, Curtis C. Harris, Ana I. Robles

Data analysis and interpretation: Reika Iwakawa, Rui Yamaguchi, Seiya Imoto, Satoru Miyano, Hirohiko Totsuka, Teruhiko Yoshida

Manuscript writing: All authors

Final approval of manuscript: All authors

Administrative support: Teruhiko Yoshida

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Figure legends

Figure 1. Numbers of genes frequently mutated in SCLC: Comparison between this study and two previous studies (a, ref 6; b, ref 7). Genes with mutation frequencies ≥10% of cases were selected in each study. Then, similarities and differences of genes selected were compared among three studies.

Figure 2. Expression of mutated alleles in significantly or frequently mutated genes in SCLC. Twenty tumors from 19 patients were analyzed by both exome sequencing and RNA sequencing. Types of mutations detected in tumors by exome sequencing are indicated by colored boxes, and expression of mutated alleles validated by RNA sequencing (RNA-seq validated) is indicated by black open squares.

Figure 3. Number of genes mutated in early and late stages of SCLCs. (A) Comparison of mutated genes between stage I tumors and stage II-IV tumors. (B) Comparison of mutated genes between primary tumors and metastases. Mutation status of three significantly mutated genes and 8 frequently mutated and expressed genes are indicated in the boxes.

Figure 4. Heterogeneity in the accumulated mutations among multiple tumors in a single SCLC patient. The primary tumor (1591T), a hilar lymph node metastasis (1592M), a liver metastasis (1594M), and a para-aortic lymph node metastasis (1595M) from a single patient were analyzed for accumulated mutations by exome sequencing. Numbers in each region indicate the numbers of genes with mutations detected in tumors. Mutation status of one of significantly mutated gene, *TP53*, and three of frequently mutated and expressed genes, *TMEM132D*, *SPTA1* and *FBN3*, are indicated in the boxes.

Table 1. Clinicopathological characteristics of 38 SCLC cases

Characteristic	No
Gender Male/Female	10/28
Age Median (range)	67 (56-89)
Smoking status Ever/Never	33/0 (5 unknown)
Brinkman index Median (range)	1000 (0-2040)
Pathological stage I/II/III/IV	10/8/10/10
Sampling at Surgery/Autopsy	36/2
Treatment before sampling -/+	31/8*

*In one case, tumors were obtained before and after chemotherapy.

Figure 1

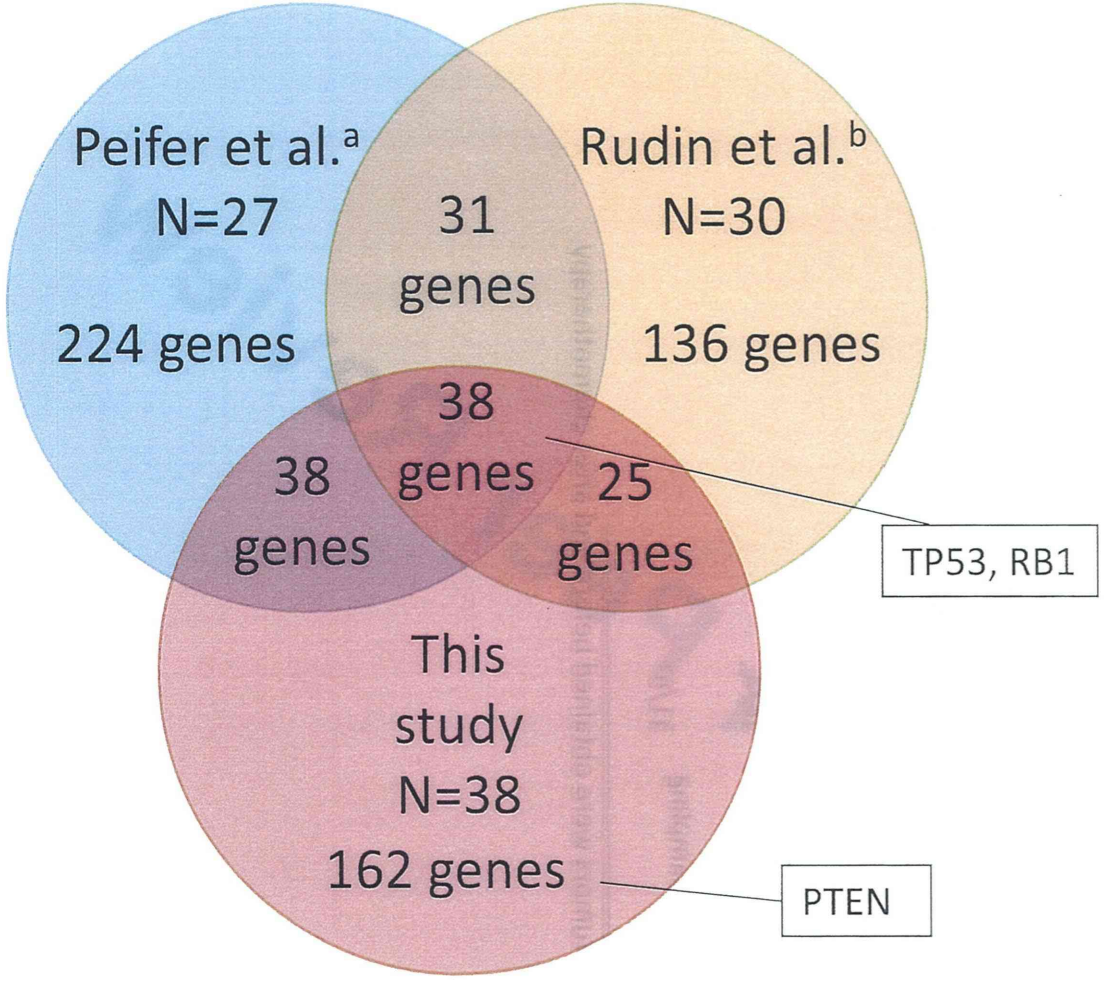

Peifer et al.[a]
N=27
224 genes
31
genes
Rudin et al.[b]
N=30
136 genes
38
genes
38
genes
25
genes
TP53, RB1
This
study
N=38
162 genes
PTEN

Figure 2

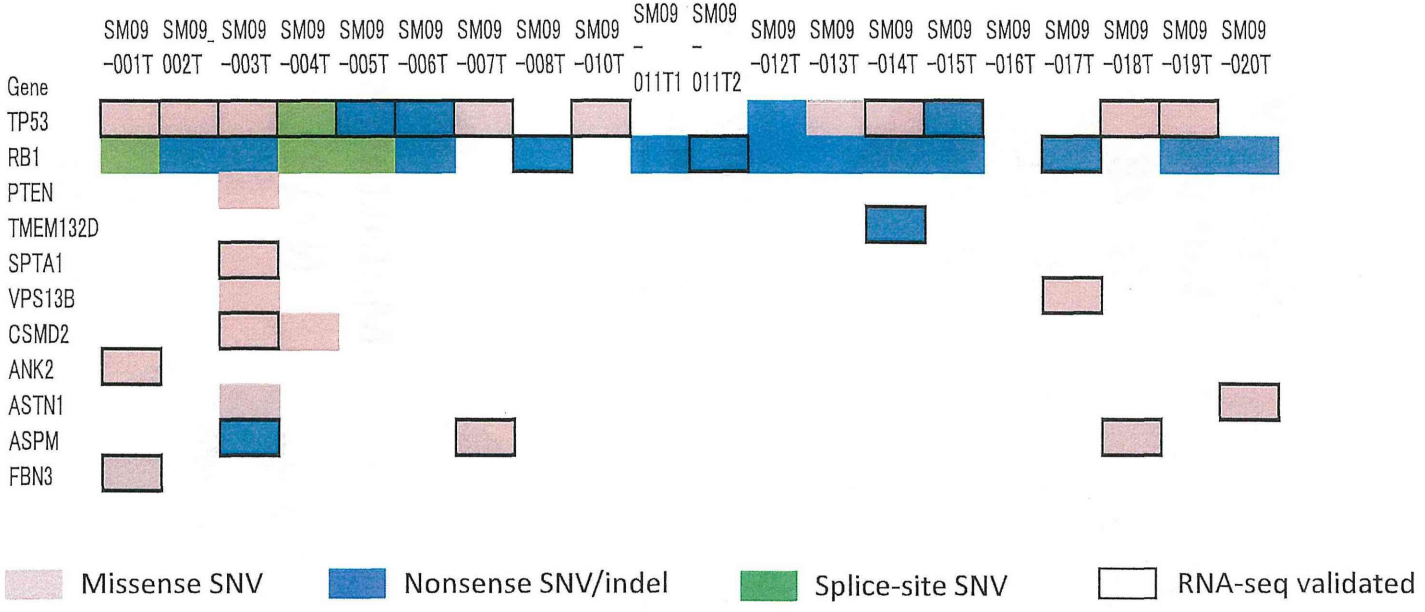
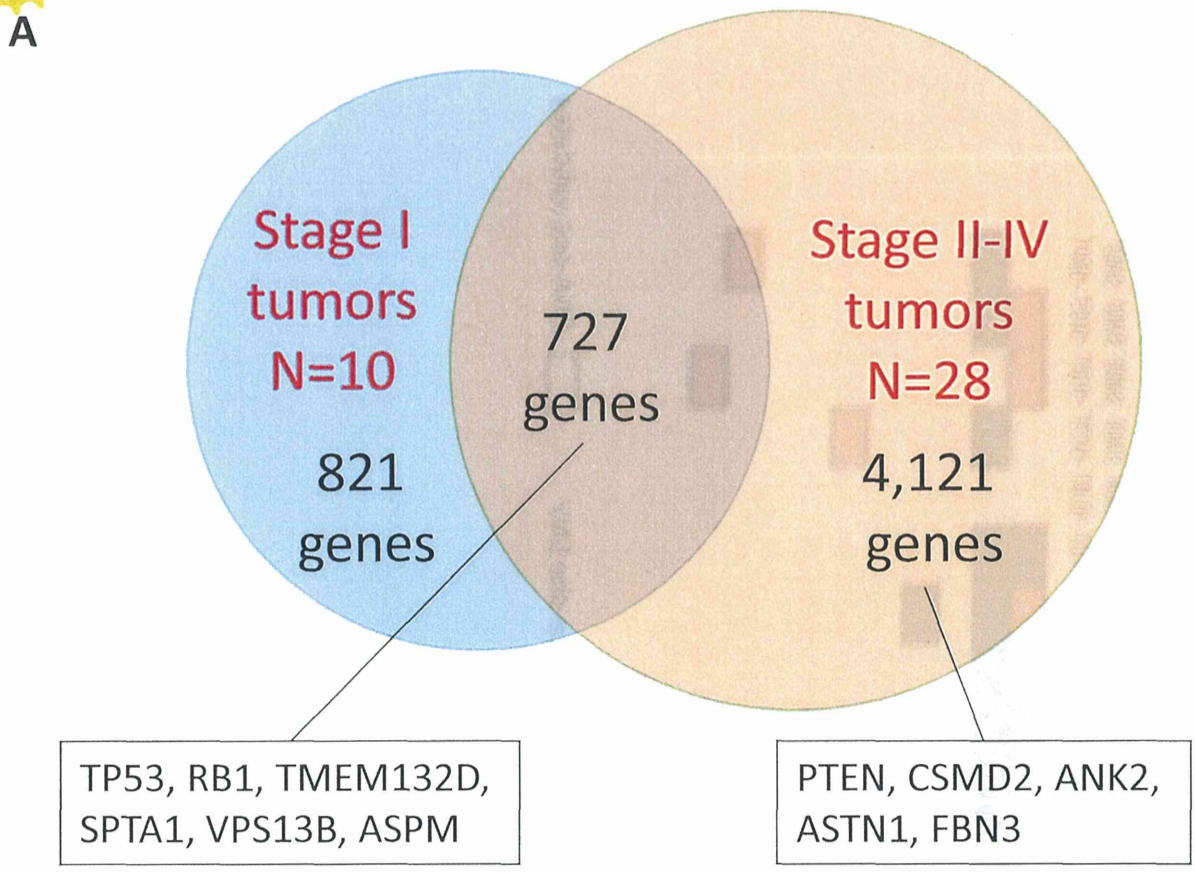

SM09 -001T
SM09_ 002T
SM09 -003T
SM09 -004T
SM09 -005T
SM09 -006T
SM09 -007T
SM09 -008T
SM09 -010T
SM09 - 011T1
SM09 - 011T2
SM09 -012T
SM09 -013T
SM09 -014T
SM09 -015T
SM09 -016T
SM09 -017T
SM09 -018T
SM09 -019T
SM09 -020T
Gene
TP53
RB1
PTEN
TMEM132D
SPTA1
VPS13B
CSMD2
ANK2
ASTN1
ASPM
FBN3
Missense SNV
Nonsense SNV/indel
Splice-site SNV
RNA-seq validated

Figure 3



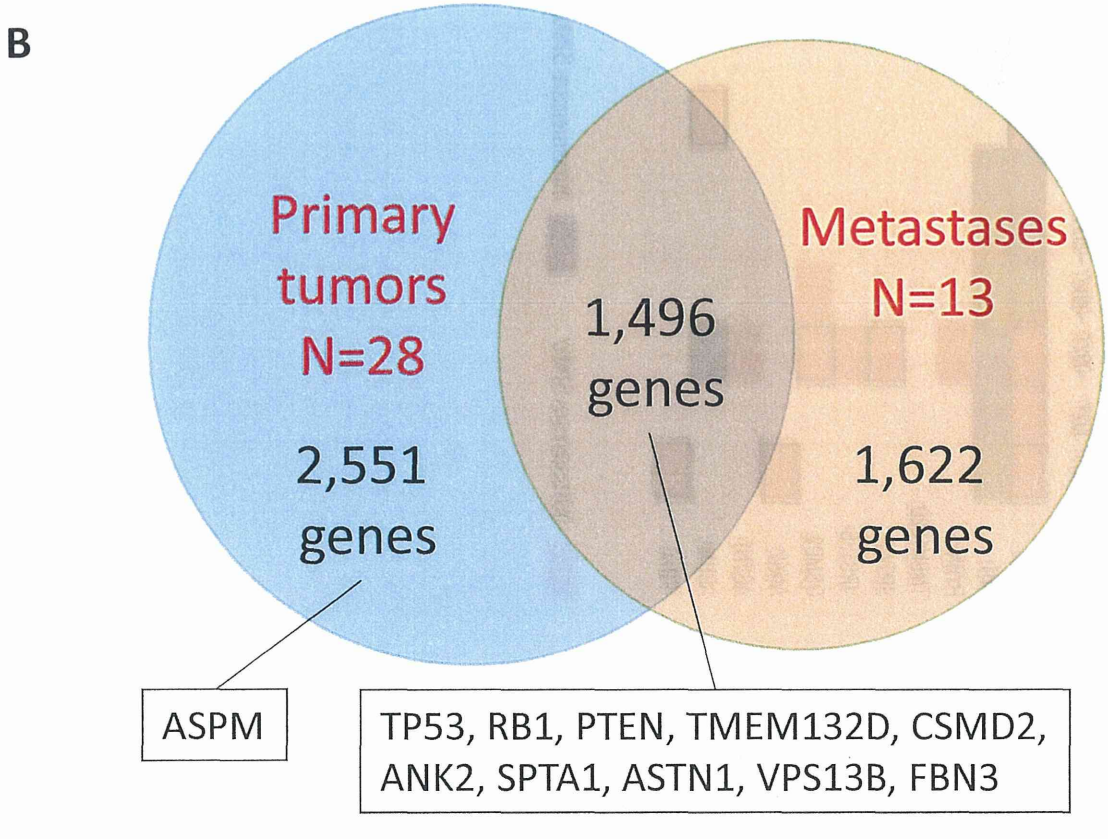
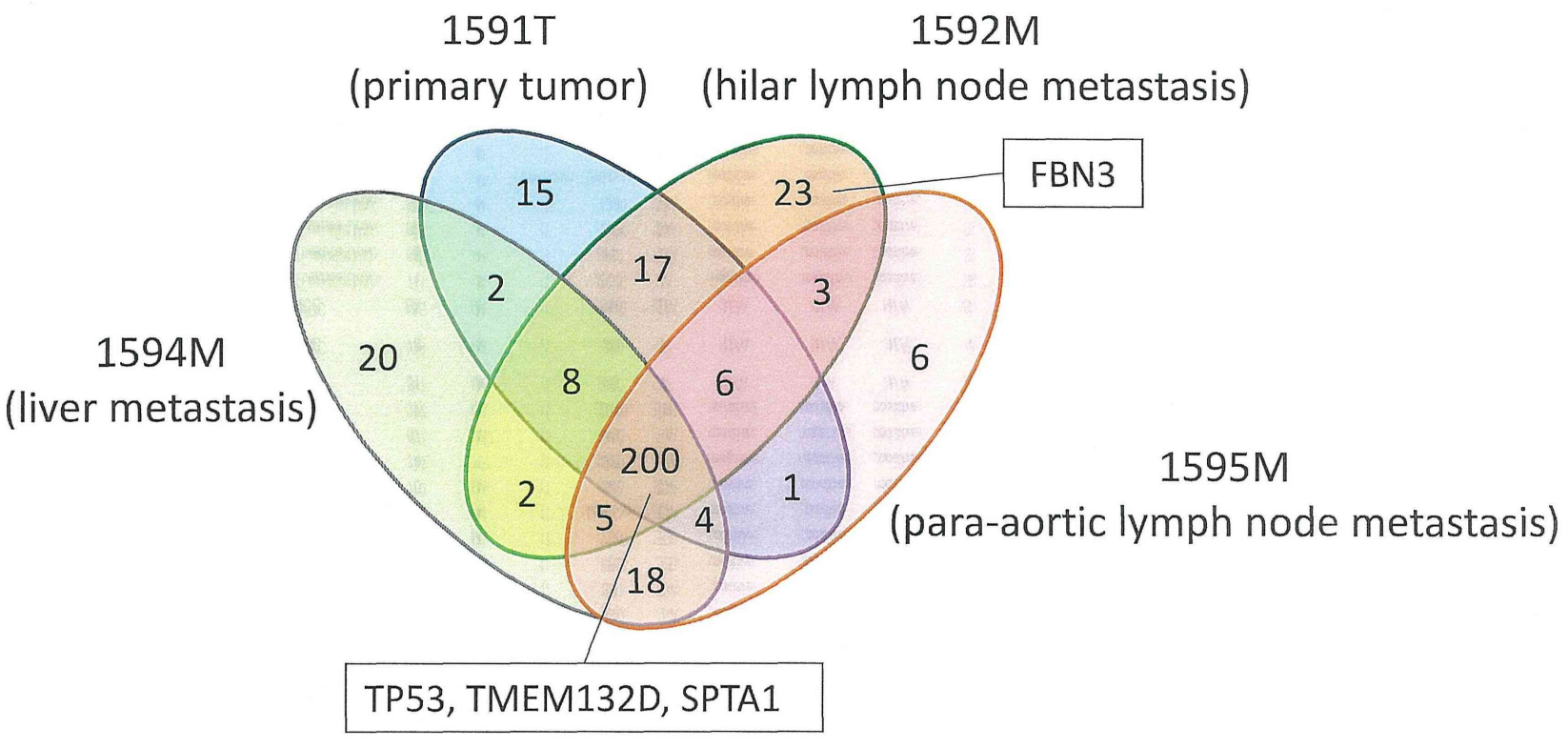


Figure 4



Supplementary Table S1. Sample information

	Sample ID	Origin of Tumor	Source	Age at Diagnosis	Gender Male = M Female = F	Smoking Never = 0 Ever = 1	Brinkman Index	Stage	Chromogranin A	Synaptophysin	NCAM	Obtained at Surgery = S Autopsy = A	Treatment Before Sampling	RNA-Seq	Chemotherapy regimen	No. of courses	Response for chemotherapy	OS (month)	Outcome Dead =
1	SM09-001T	Lung (P)	NCC	75	F	Unknown	Unknown	IIA	positive	positive	positive	S	No	Yes	Non	-	-	20.0	1
2	SM09-002T	Lung (P)	NCC	89	M	1	1020	IA	negative	negative	negative	S	No	Yes	Non	-	-	26.6	1
3	SM09-003T	Lung (P)	NCC	79	F	1	680	IIIB	positive	positive	positive	S	No	Yes	CBDCA+VP16	3	-	64.5	0
4	SM09-004T	Lung (P)	NCC	70	F	1	1000	IIIB	positive	positive	positive	S	No	Yes	Non	-	-	19.7	1
5	SM09-005T	Lung (P)	NCC	59	M	1	660	IA	positive	positive	positive	S	No	Yes	Non	-	-	29.6	1
6	SM09-006T	Lung (P)	NCC	75	M	1	800	IIB	negative	negative	positive	S	No	Yes	Non	-	-	1.1	0
7	SM09-007T	Lung (P)	NCC	65	M	1	1350	IA	positive	positive	positive	S	No	Yes	Non	-	-	1.5	1
8	SM09-008T	Lung (P)	NCC	64	M	1	1000	IIA	positive	positive	positive	S	No	Yes	CDDP+CPT-11	4	-	9.1	1
9	SM09-010T	LN (M)	NCC	67	F	Unknown	Unknown	IIA	positive	positive	positive	S	No	Yes	CDDP+CPT-11	4	-	67.0	0
10	SM09-011T1/011T2	Lung (P)/Rib (M)	NCC	66	M	1	900	IIIA	positive	positive	positive	S	No	Yes	CDDP+CPT-11	4	-	19.7	1
11	SM09-012T	Lung (P)	NCC	63	M	1	400	IA	positive	positive	positive	S	No	Yes	Non	-	-	97.7	0
12	SM09-013T	Lung (P)	NCC	76	M	1	301	IA	positive	positive	positive	S	No	Yes	Non	-	-	26.2	0
13	SM09-014T	Lung (P)	NCC	57	M	1	1560	IB	positive	positive	positive	S	No	Yes	Non	-	-	92.0	0
14	SM09-015T	Lung (P)	NCC	67	M	1	1290	IIB	positive	positive	positive	S	No	Yes	Non	-	-	9.7	0
15	SM09-016T	Lung (P)	NCC	47	M	1	Unknown	IIIA	positive	positive	positive	S	No	Yes	CDDP+CPT-11	4	-	47.8	1
16	SM09-017T	Lung (P)	NCC	70	M	1	800	IIIA	positive	positive	positive	S	No	Yes	Non	-	-	78.8	1
17	SM09-018T	Lung (P)	NCC	74	F	1	980	IA	negative	negative	positive	S	No	Yes	CDDP+CPT-11	4	-	67.7	0
18	SM09-019T	Lung (P)	NCC	67	M	1	940	IA	positive	negative	positive	S	No	Yes	CDDP+CPT-11	4	-	54.8	0
19	SM09-020T	Lung (P)	NCC	72	M	1	2040	IIB	positive	positive	positive	S	No	Yes	CBDCA+VP16	4	-	22.9	0
20	1581M/1582M	Liver (M)/LN (M)	NCC	61	M	1	800	IV	N/A	N/A	N/A	A	CT + RT	No	CDDP+VP16	4	PR	9.0	1
21	1591T/1592M/1594M/1595M	Lung (P)/Hilar LN (M) /Liver (M)/Para-aortic LN (M)	NCC	78	M	1	360	IV	N/A	N/A	N/A	A	CT	No	CBDCA	3	PR	10.8	1
22	1601T/1602M	Lung (P)/LN (M)	NCC	65	M	1	1840	IIIA	N/A	N/A	N/A	S	No	No	Non	-	-	1.1	1
23	THB-Lu-1T	Lung (P)	Tsukuba Univ.	71	M	1	2000	IA	negative	negative	positive	S	No	No	Non	-	-	28.4	1
24	THB-Lu-2T	Lung (P)	Tsukuba Univ.	68	M	1	960	IIIA	positive	positive	positive	S	No	No	CBDCA + VP16	4	-	28.4	1
25	THB-Lu-3T	Lung (P)	Tsukuba Univ.	68	M	1	1200	IIIA	positive	positive	positive	S	No	No	Non	-	-	5.1	1
26	THB-Lu-4T	Lung (P)	Tsukuba Univ.	63	M	1	1380	IIIA	positive	positive	positive	S	No	No	CDDP+VP16	4	-	25.4	1
27	THB-Lu-5T	Lung (P)	Tsukuba Univ.	66	M	Unknown	Unknown	IIIA	positive	positive	positive	S	CT	No	CBDCA+PEM	2	Unknown	30.4	0
28	SBM-T04	Brain (M)	Saitama Univ.	73	M	1	1060	IV	negative	positive	N/A	S	No	No	Non	-	-	4.6	1
29	SBM-T08	Brain (M)	Saitama Univ.	58	M	1	1000	IV	negative	positive	N/A	S	No	No	Non	-	-	0.6	1
30	SBM-T17	Brain (M)	Saitama Univ.	66	M	1	1380	IV	N/A	negative	N/A	S	No	No	Non	-	-	22.3	0
31	SBM-T37	Brain (M)	Saitama Univ.	66	F	1	520	IV	positive	positive	N/A	S	No	No	Non	-	-	24.1	1
32	SBM-T40	Brain (M)	Saitama Univ.	76	F	Unknown	Unknown	IV	positive	positive	N/A	S	No	No	Non	-	-	0.5	0
33	M153T	Brain (M)	NCC	72	F	Unknown	Unknown	IV	N/A	N/A	N/A	S	CT + S +RT	No	CDDP+CPT-11/AMR	1/4	CR	31.9	1
34	M189T	Brain (M)	NCC	56	F	1	Unknown	IV	positive	positive	positive	S	CT + RT	No	CDDP+CPT-11/AMR/PEI	3/1/5	CR/PD/PD	29.6	1
35	M288T	Brain (M)	NCC	58	M	1	1170	IV	positive	positive	positive	S	RT + S + CT	No	CDDP+CPT-11	4	Unknown	22.7	1
36	11169T	Lung (P)	US	76	M	1	1220	IB	N/A	N/A	N/A	S	No	No	Non	-	-	101.7	1
37	12878T	Lung (P)	US	70	M	1	1160	IIB	N/A	positive	N/A	S	No	No	Non	-	-	11.3	1
38	19100T	Lung (P)	US	58	F	1	1140	IIA	N/A	N/A	N/A	S	CT	No	Unknown	Unknown	Unknown	14.5	1

P = primary tumor
M = metastatic tumor
LN = lymph node

NCC = National Cancer Center
US = United States

CT = Chemotherapy
RT = Radiotherapy

CBDCA = Carboplatin
VP16 = Etoposide
CDDP = Cisplatin
PEM = Pemetrexed
AMR = Amrubicin

Supplementary Table S3. List of genes frequently mutated in small cell lung cancer

		Total	N=95	This study	N=38	Peifer et al. (ref. 6)	N=27	Rudin et al. (ref. 7)	N=30
No	Gene	#of mutated case	Freq (%)	#of mutated case	Freq (%)	#of mutated case	Freq (%)	#of mutated case	Freq (%)
1	TP53	79	83.2	30	78.9	24	88.9	25	83.3
2	RB1	63	66.3	28	73.7	18	66.7	17	56.7
3	PTEN	9	9.5	5	12.5	2	7.4	2	6.7
4	LRP1B	41	43.2	14	36.8	13	48.1	14	46.7
5	TTN	35	36.8	18	47.4	10	37.0	7	23.3
6	CSMD3	35	36.8	12	31.6	10	37.0	13	43.3
7	USH2A	34	35.8	15	39.5	12	44.4	7	23.3
8	MUC17	26	27.4	10	26.3	8	29.6	8	26.7
9	SYNE1	24	25.3	10	26.3	6	22.2	8	26.7
10	CSMD2	20	21.1	9	23.7	7	25.9	4	13.3
11	COL11A1	20	21.1	5	13.2	8	29.6	7	23.3
12	FLG	19	20.0	7	18.4	7	25.9	5	16.7
13	PKHD1	19	20.0	6	15.8	9	33.3	4	13.3
14	SPHKAP	19	20.0	7	18.4	8	29.6	4	13.3
15	SI	18	18.9	6	15.8	7	25.9	5	16.7
16	GRIN2A	17	17.9	7	18.4	5	18.5	5	16.7
17	TNN	16	16.8	6	15.8	7	25.9	3	10.0
18	FAM135B	16	16.8	7	18.4	5	18.5	4	13.3
19	XIRP2	16	16.8	9	23.7	4	14.8	3	10.0
20	NAV3	15	15.8	6	15.8	4	14.8	5	16.7
21	COL12A1	15	15.8	5	13.2	5	18.5	5	16.7
22	COL22A1	15	15.8	4	10.5	5	18.5	6	20.0
23	DNAH9	15	15.8	4	10.5	6	22.2	5	16.7
24	PLXNA4	15	15.8	9	23.7	3	11.1	3	10.0
25	CDH10	15	15.8	6	15.8	6	22.2	3	10.0
26	ANK2	14	14.7	5	13.2	5	18.5	4	13.3
27	TMEM132D	14	14.7	4	10.5	7	25.9	3	10.0
28	CDH18	14	14.7	7	18.4	4	14.8	3	10.0
29	DNAH5	14	14.7	6	15.8	3	11.1	5	16.7
30	SPTA1	14	14.7	7	18.4	4	14.8	3	10.0
31	HCN1	13	13.7	4	10.5	5	18.5	4	13.3
32	LAMA2	13	13.7	4	10.5	5	18.5	4	13.3
33	LRRC7	12	12.6	4	10.5	4	14.8	4	13.3
34	GPR112	11	11.6	5	13.2	3	11.1	3	10.0
35	ASTN1	11	11.6	4	10.5	3	11.1	4	13.3
36	ASPM	11	11.6	4	10.5	4	14.8	3	10.0
37	VPS13B	11	11.6	4	10.5	4	14.8	3	10.0
38	FBN3	10	10.5	4	10.5	3	11.1	3	10.0
39	MYH1	10	10.5	4	10.5	3	11.1	3	10.0

Supplementary Table S4. Types of TP53, RB1 and PTEN gene mutations detected in 38 SCLC cases

No	Sample name	TP53	RB1	PTEN
1	SM09-001T	NM_000546:exon5:c.G473T:p.R158L	NM_000321:exon16:c.1422-2A>T	—
2	SM09-002T	NM_000546:exon5:c.A536G:p.H179R	NM_000321:exon20:c.2033_2034insT:p.H678fs	—
3	SM09-003T	NM_000546:exon8:c.G814A:p.V272M	NM_000321:exon17:c.1621delA:p.N541fs	NM_000314:exon5:c.T463C:p.Y155H
4	SM09-004T	NM_000546:exon6:c.376-1G>T	NM_000321:exon24:c.2520+1G>T	—
5	SM09-005T	NM_000546:exon6:c.G610T:p.E204X	NM_000321:exon16:c.1422-2A>G	—
6	SM09-006T	NM_000546:exon4:c.262_263insA:p.A88fs	NM_000321:exon20:c.G2043A:p.W681X	—
7	SM09-007T	NM_000546:exon7:c.G746T:p.R249M	—	—
8	SM09-008T	—	NM_000321:exon13:c.G1267T:p.G423X	—
9	SM09-010T	NM_000546:exon5:c.A536T:p.H179L, exon6:c.559+1G>C	—	—
10	SM09-011T1/ SM09-011T2	—	NM_000321:exon24:c.C2501G:p.S834X	—
11	SM09-012T	NM_000546:exon6:c.652delG:p.V218fs	NM_000321:exon11:c.C1072T:p.R358X	—
12	SM09-013T	NM_000546:exon7:c.G733C:p.G245R	NM_000321:exon23:c.2436_2439del:p.812_813del	—
13	SM09-014T	NM_000546:exon6:c.A583T:p.I195F	NM_000321:exon22:c.2218_2219del:p.740_740del	—
14	SM09-015T	NM_000546:exon5:c.C548G:p.S183X	NM_000321:exon9:c.G937T:p.E313X	—
15	SM09-016T	—	—	—
16	SM09-017T	—	NM_000321:exon17:c.1580_1581insT:p.D527fs	—
17	SM09-018T	NM_000546:exon8:c.G818C:p.R273P	—	—
18	SM09-019T	NM_000546:exon8:c.G818T:p.R273L	NM_000321:exon3:c.370_371del:p.124_124del	—
19	SM09-020T	—	NM_000321:exon19:c.1868_1883del:p.623_628del	—
20	1581M/1582M	—	—	—
21	1591T/1592M/ 1594M/1595M	NM_000546:exon6:c.G592T:p.E198X	—	—
22	1601T/1602M	NM_000546:exon4:c.96+1G>T	—	NM_000314:exon9:c.C1126T:p.H376Y, exon7:c.711delG:p.K237fs
23	THB_Lu_1T	NM_000546:exon6:c.T660G:p.Y220X	NM_000321:exon17:c.1695+1G>T	—
24	THB_Lu_2T	NM_000546:exon4:c.C112T:p.Q38X	NM_000321:exon19:c.1917_1918insA:p.Q639fs	—
25	THB_Lu_3T	NM_000546:exon4:c.162_163insC:p.T55fs	NM_000321:exon24:c.2490-1G>A	—
26	THB_Lu_4T	NM_000546:exon6:c.G661T:p.E221X	—	—
27	THB_Lu_5T	NM_000546:exon7:c.G743T:p.R248L	NM_000321:exon13:c.G1318T:p.E440X	NM_000314:exon5:c.G448T:p.E150X
28	SBM_T04	NM_000546:exon7:c.A707G:p.Y236C	NM_000321:exon12:c.1128-2A>T	—
29	SBM_T08	—	NM_000321:exon13:c.A1234T:p.K412X	NM_000314:exon6:c.G518T:p.R173L
30	SBM_T17	NM_000546:exon6:c.G638T:p.R213L	NM_000321:exon10:c.1011delG:p.L337fs, exon10:c.G1011T:p.L337F	—
31	SBM_T37	NM_000546:exon8:c.782+1G>C	NM_000321:exon2:c.G157T:p.E53X	—
32	SBM_T40	NM_000546:exon5:c.529_546del:p.177_182del	NM_000321:exon17:c.G1675T:p.E559X	—
33	M153T	NM_000546:exon6:c.G592T:p.E198X	—	—
34	M189T	NM_000546:exon9:c.C991T:p.Q331X	NM_000321:exon23:c.2330_2331insT:p.P777fs	—
35	M288T	NM_000546:exon7:c.G733T:p.G245C	NM_000321:exon22:c.C2273A:p.S758X	NM_000314:exon5:c.G316T:p.E106X
36	11169T	NM_000546:exon8:c.G839T:p.R280I	NM_000321:exon14:c.1333-1G>C	—
37	12878T	NM_000546:exon5:c.G469T:p.V157F	—	—
38	19100T	NM_000546:exon5:c.G469T:p.V157F	NM_000321:exon21:c.2211+1G>A	—

Supplementary Table S5. Significantly mutated genes in three studies

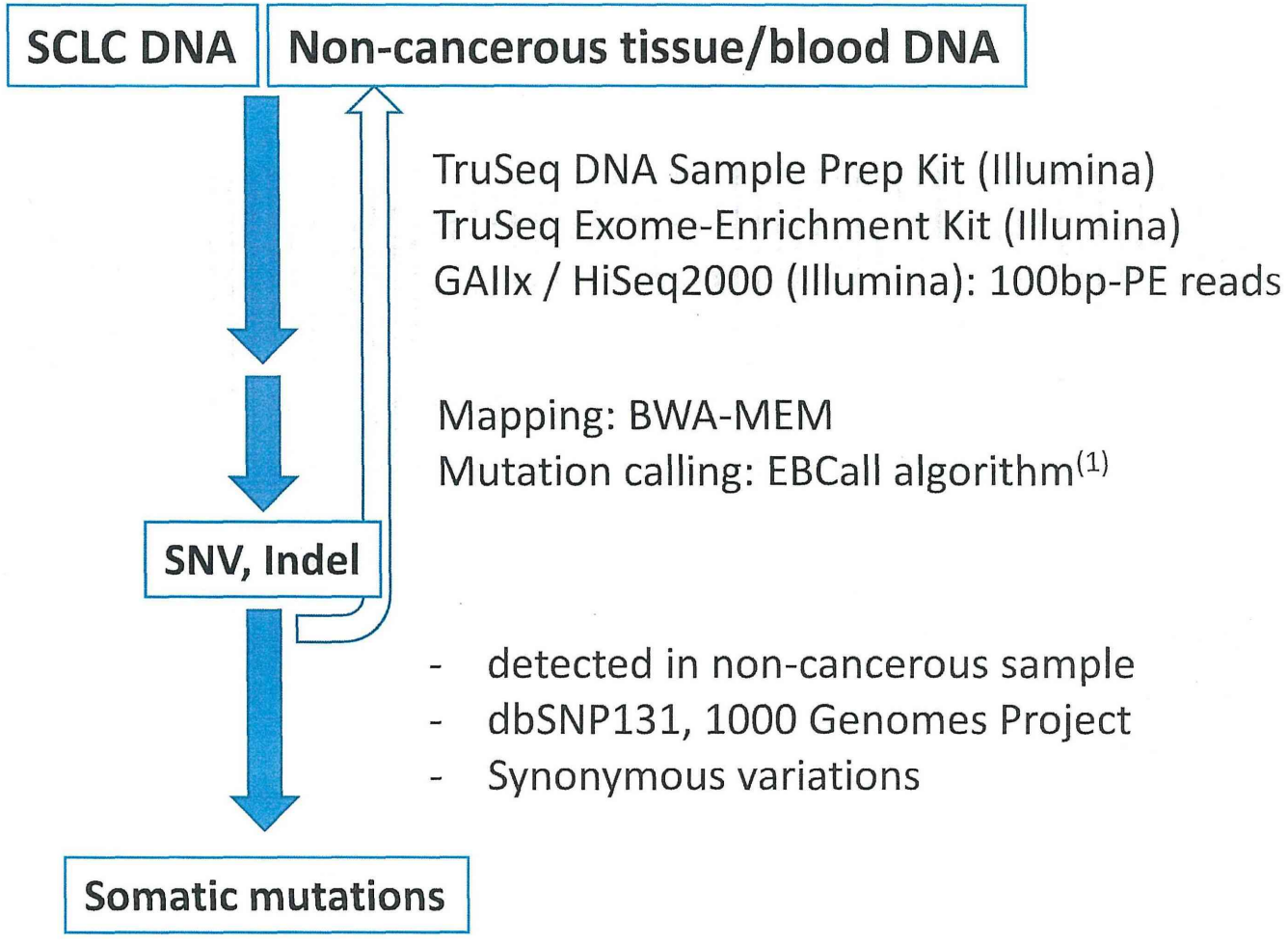
No	Gene	This study	Peifer et al. (ref. 6)	Rudin et al. (ref. 7)
1	TP53	v	v	v
2	RB1	v	v	v
3	PTEN	v		
4	PRDM9		v	
5	TFAP2D		v	
6	TKTL2		v	
7	OR10G7		v	
8	OR11L1		v	
9	ZNF536		v	
10	TMEM132D		v	v
11	ZNF521		v	
12	TUBA3C		v	
13	HCN1		v	
14	SLURP1		v	
15	TNN		v	
16	FAM133A		v	
17	CDH10		v	
18	SPHKAP		v	
19	COL11A1		v	
20	NCAM2		v	
21	XPNPEP2		v	
22	OR5B17		v	
23	FOXE1		v	
24	COL22A1			v
25	ELAVL2			v
26	RASSF8			v
27	CNTNAP2			v
28	BCLAF1			v
29	GRM8			v
30	KIF21A			v
31	GRIK3			v
32	C17orf108			v
33	RUNX1T1			v
34	PLSCR4			v
35	CDYL			v
36	RIMS2			v
37	ZDBF2			v
38	KHSRP			v
39	SATB2			v
40	COL4A2			v
41	DIP2C			v
42	ADCY1			v

Supplementary Table S6. Mutation spectra of significantly mutated genes

Gene	Name	Location	Alterations	SM09-001T	SM09-002T	SM09-003T	SM09-004T	SM09-005T	SM09-006T	SM09-007T	SM09-008T	SM09-010T	SM09-011T1/011T2	SM09-012T	SM09-013T	SM09-014T	SM09-015T	SM09-016T	SM09-017T	SM09-018T	SM09-019T	SM09-020T	THB_Lu_1T	THB_Lu_2T	THB_Lu_3T	THB_Lu_4T	THB_Lu_5T	11169T	12878T	19100T	M153T	M189T	M288T	SBM_T04	SBM_T08	SBM_T17	SBM_T37	SBM_T40	1581M/1582M	1591T/1592M/1594M/1595M	1601T/1602M
TP53	tumor protein p53	17p13.1	Mutation	p.R158L	p.H179R	p.V272M	c.376-1G	p.E204X	p.A88fs	p.R249M		c.559+1G		p.Y218fs	p.G245R	p.I195F	p.S183X			p.R273P	p.R273L		p.Y220X	p.Q38X	p.T55fs	p.E221X	p.R248L	p.R280I	p.V157F	p.V157F	p.E198X	p.Q331X	p.G245C	p.Y236C		p.R213L	c.782+1G	p.177_182del		p.E198X	c.96+1G
			Variant frequency	0.91	0.89	0.88	0.89	0.38	0.87	1.00		0.45, 0.56		0.82	0.87	1.00	1.00			0.64	0.67		0.39	0.58	0.85	0.13	0.95	0.98	0.91	0.91	0.13	0.75	0.97	0.49		0.83	0.73	0.57		0.89	0.85
			Copy number	LOH	LOH	LOH	LOH	LOH	LOH	LOH	LOH	Gain	LOH	LOH	LOH	LOH	LOH		LOH	LOH	LOH	LOH	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
RB1	retinoblastoma 1	13q14.2	Mutation	c.1422-2	p.H678fs	p.N541fs	c.2520+1	c.1422-2	p.W681X		p.G423X		p.S834X	p.R358X	p.812_813	p.740_740	p.E313X		p.D527fs		p.124_124	p.623_623	c.1695+1	p.Q639fs	c.2490-1		p.E440X	c.1333-1		c.2211+1		p.P777fs	p.S758X	c.1128-2	p.K412X	p.L337fs,	p.E32X	p.E359X			
			Variant frequency	0.87	0.85	0.63	0.79	0.41	0.89		0.92		0.88	0.89	0.56	0.45	0.98		0.68		0.57	0.86	0.41	0.34	0.85		0.91	0.98		0.76		0.57	1.00	0.46	0.83	0.79, 0.26	0.66	0.63			
			Copy number	LOH	LOH	LOH	LOH		LOH	LOH	LOH	LOH	LOH	LOH	LOH	LOH	Gain	LOH	LOH		LOH	LOH	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PTEN	phosphatase and tensin homolog	10q23.3	Mutation			p.Y155H																				p.E150X					p.E106X		p.R173L						p.H376Y,
			Variant frequency			0.62																				0.92					0.98		0.70						0.80, 0.83
			Copy number	LOH		LOH	LOH		LOH		Loss		T2:LOH	LOH			LOH					Gain	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TMEM132D	transmembrane protein 132D	12q24.33	Mutation													p.Q763X								p.A694T													p.M614I		p.P1038L	
			Variant frequency													0.37								0.35													0.39		1.00	
			Copy number						Gain				LOH			Gain	LOH					Gain	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SPTA1	spectrin, alpha, erythrocytic 1	1q21	Mutation			p.I2231M																	p.A2025E		p.I1326T		p.D2084E				p.V1685G					c.1678-1			p.P1040L	
			Variant frequency			0.37																	0.34		0.56		0.45				0.39					0.56			0.43	
			Copy number		Gain	Gain	Gain		Gain			Gain	T2:Gain	Gain	Gain	Gain		Gain	Gain		Gain	Gain	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
VPS13B	vacuolar protein sorting 13 homolog B	8q22.2	Mutation			p.A2041S													p.Y324C				p.L631V											p.G1637C							
			Variant frequency			0.40													0.44				0.31											0.57, 0.21	0.24						
			Copy number				Gain	Gain	LOH	Gain			T1:Gain	Gain		Gain	Gain		Gain		Gain		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

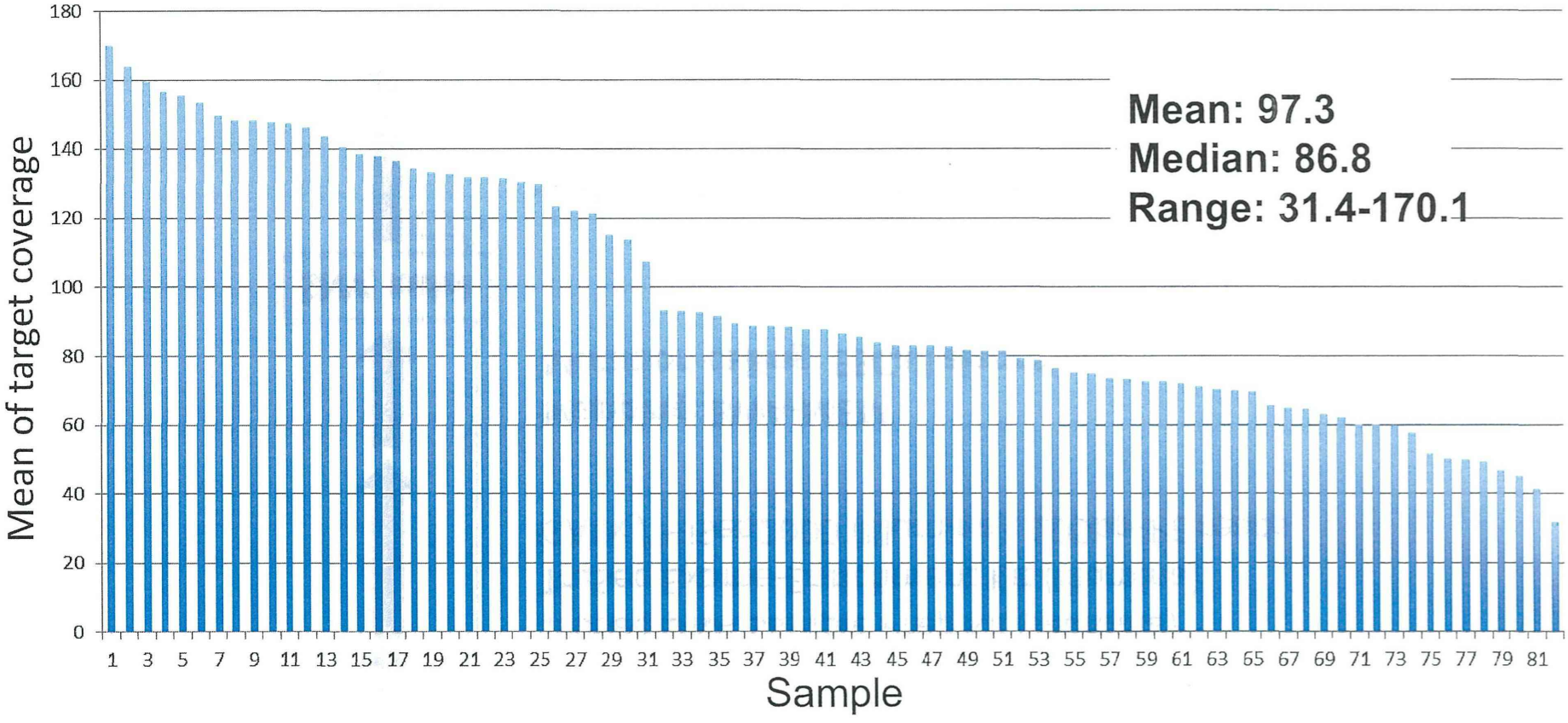
inactivationg mutation (nonsense mutations, frameshift mutations and mutations at exon-intron boundary)
variant frequency > 50%
LOH detected by SNP array analysis
Gain detected by SNP array analysis

Supplementary Figure S1. Exome Sequencing and Data Processing

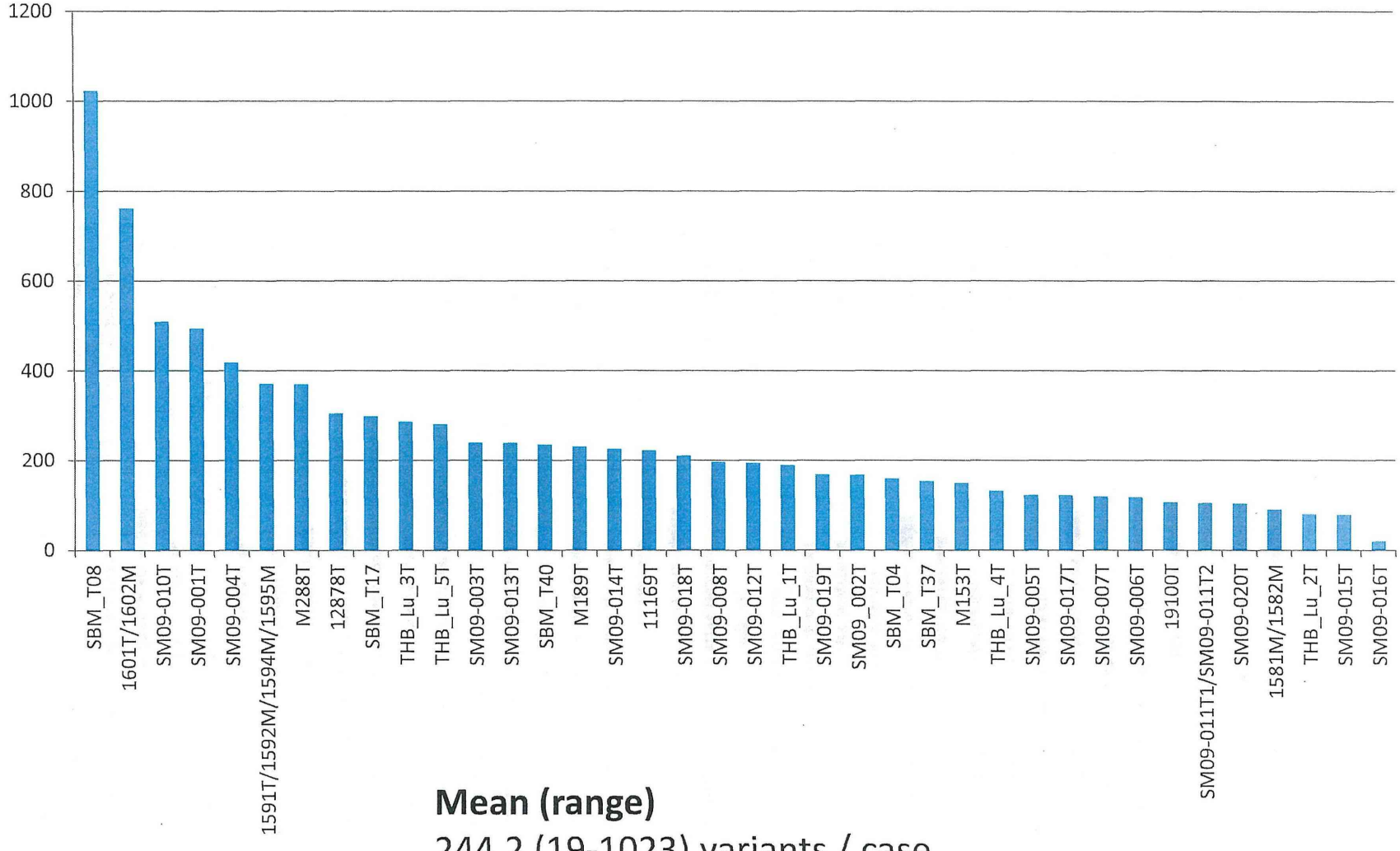


(1), Shiraishi Y, et al., An empirical Bayesian framework for somatic mutation detection from cancer genome sequencing data. Nucleic Acids Res. 2013;41:e89.

Supplementary Figure S2. Mean of Target Coverage in 38 SCLC Cases



Supplementary Figure S3. Numbers of Somatic Mutations Detected in 38 SCLC Cases

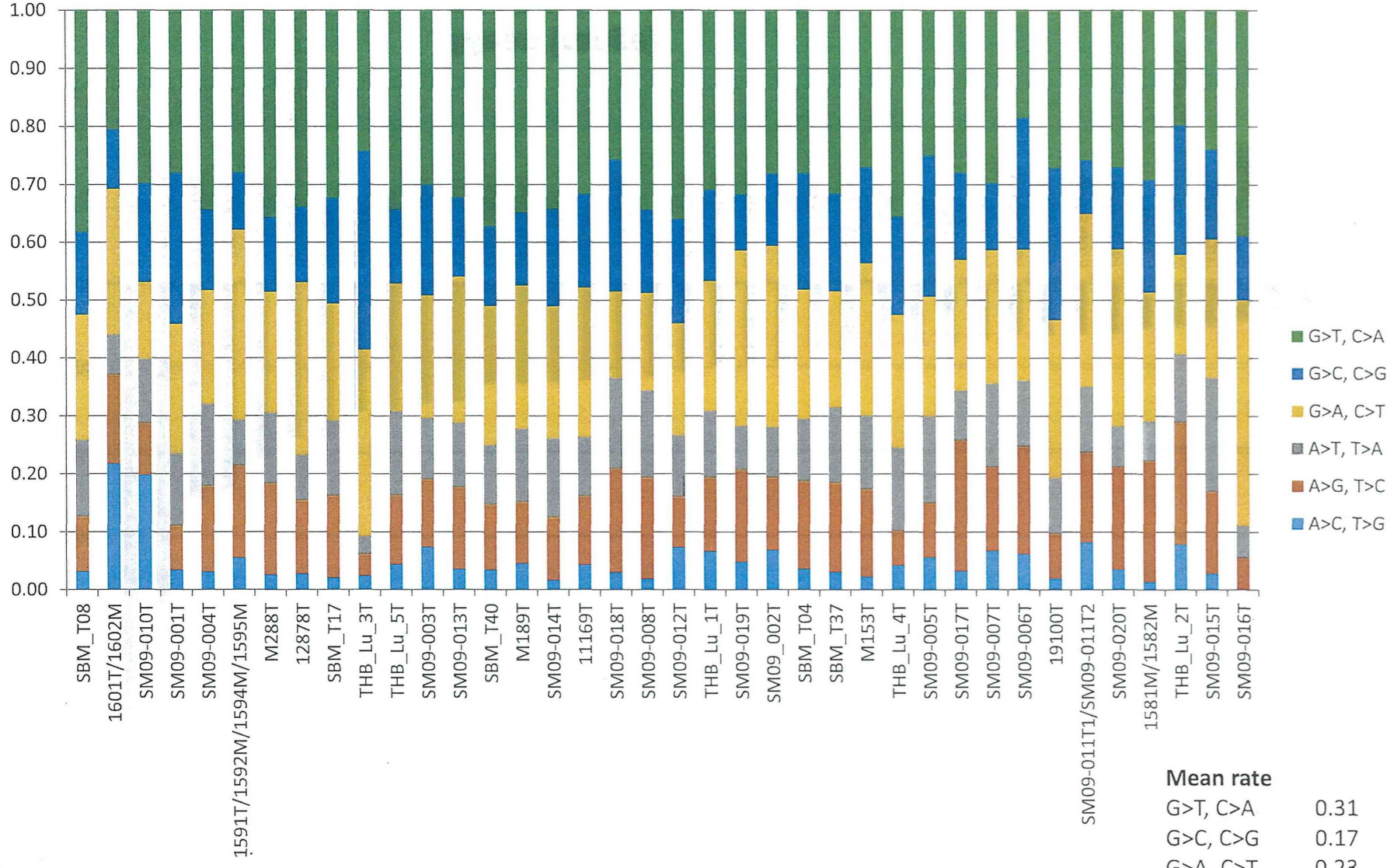


Mean (range)

244.2 (19-1023) variants / case

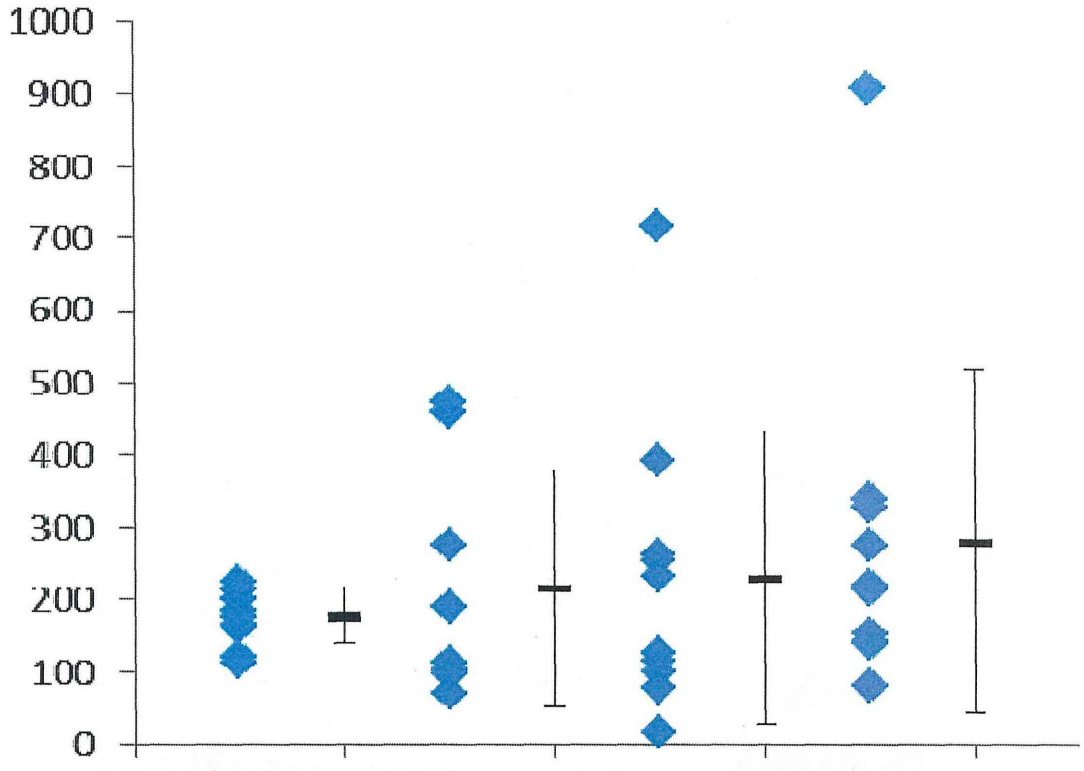
7.4 (0.6-30.8) variants / Mb

Supplementary Figure S4. Base-level Transitions and Transversions in 38 SCLC Cases



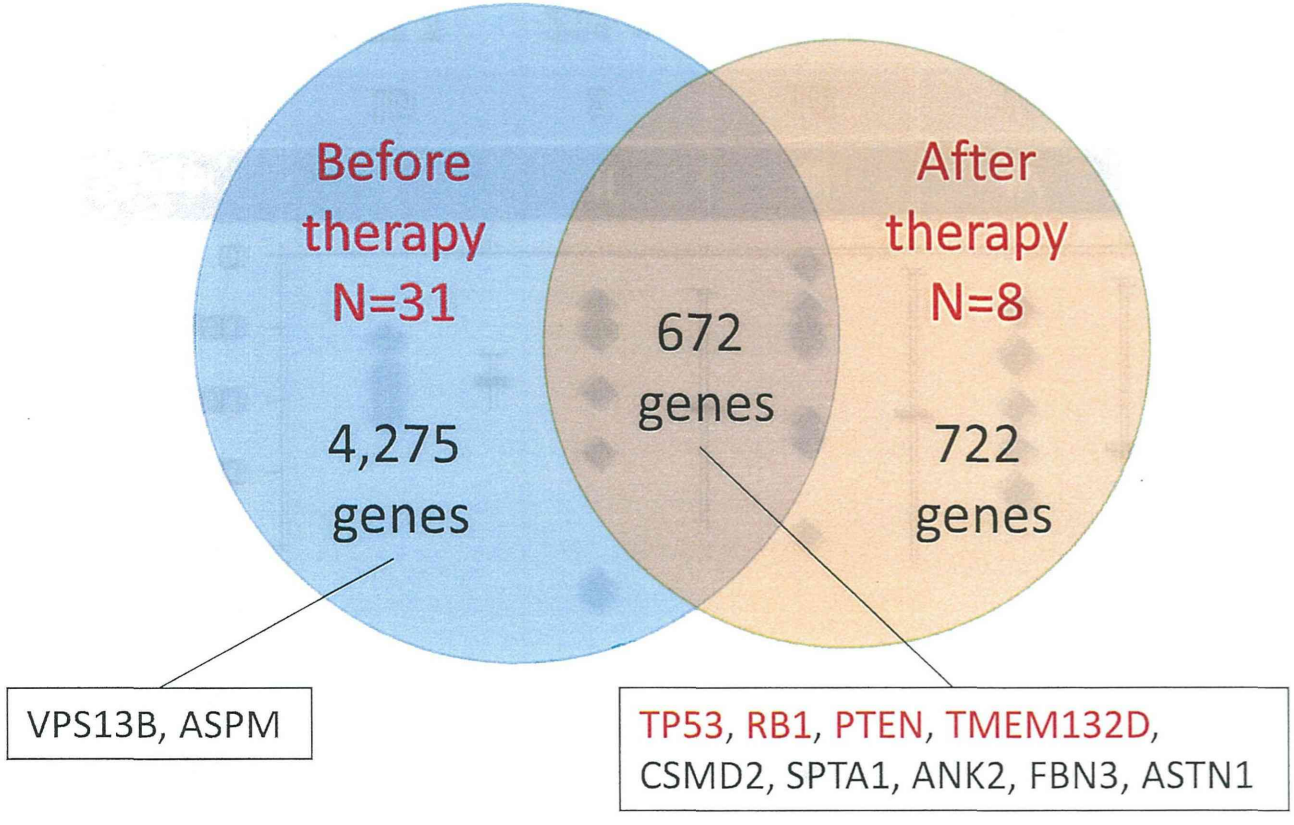
Mean rate	
G>T, C>A	0.31
G>C, C>G	0.17
G>A, C>T	0.23
A>T, T>A	0.11
A>G, T>C	0.12
A>C, T>G	0.05

Supplementary Figure S5. Numbers of Somatically Mutated Genes in SCLC According to the TNM Staging



Stage	I	II	III	IV
N	10	8	10	10
Mean	177.7	215.1	229.9	280.6

Supplementary Figure S6. Comparison of Mutated Genes Between Tumors Obtained Before and After Chemotherapy/Radiotherapy



Mutated genes / sample (average)	230.7	195.0	(*P*=0.50 by Student's *t*-test)