



Figure S1 Comparisons of somatic mutation frequencies. Significant differences between the 162 MPLC probands and 3,243 LUAD patients are shown (Mann-Whitney U test). One star represents a P value <0.05, two stars represent a P value <0.01, and three stars represent a P value <0.001.

Table S1 The frequencies of *EGFR* mutations in 366 MPLC tumor lesions

Exon	Type	SMF in 366 MPLC lesions (%)	
Total		93 (25.41) (102-9)	
18	p.G719A	0	
	p.G719S	1 (0.27)	
	p.G719C	0	
19del	p.746_749del	0	
	p.747_753del	0	
	p.745_750del	10 (2.73)	
	p.746_750del	9 (2.46)	
	p.747_751del	2 (0.55)	
	p.746_751del	2 (0.55)	
	p.751_758del	1 (0.27)	
	p.747_752del	4 (1.09)	
	p.741_741del	0	
	p.755_756del	0	
	p.A743delinsAIKIPVD	0	
	p.746_752del	0	
	p.749_754del	0	
	p.746_746del	0	
	p.752_759del	0	
	p.745_748del	0	
	p.M766delinsMASM	0	
	20	p.A767delinsASVA	0
		p.V769delinsVASV	7 (1.91)
p.D770delinsDSVD		5 (1.37)	
p.N771delinsNPHPH		0	
p.P772delinsPP		0	
p.H773delinsHH		0	
p.H773delinsHNPH		0	
p.S768I		7 (1.91)	
p.S768N		2 (0.55)	
p.R776H		0	
p.R776G		0	
p.R776C		0	
p.L788V		1 (0.27)	
p.C781Y		1 (0.27)	
p.T790M		4 (1.09)	
Q791*	1 (0.27)		
p.C797S	0		
p.V843I	4 (1.09)		
21	p.L858Q	0	
	p.L858R	42 (11.48)	
	p.L861Q	0	
	p.L861G	0	

SMF, somatic mutation frequencies.

Table S2 Information regarding smoking status and sex in 162 MPLC and 3,243 LUAD patients

	162 MPLC		3,243 sporadic LUAD		Chi-square test
	Smoker	Nonsmoker	Smoker	Nonsmoker	
Smoking status	44/162 (27.16%)	118/162 (72.84%)	1118/3243 (34.47%)	2125/3243 (65.53%)	P=0.055
<i>EGFR</i> SMF*	13/44 (29.55%)	61/118 (51.69%)	453/1118 (40.52%)	1361/2125 (64.05%)	
<i>EGFR</i> SMF	11/44 (25.00%)	52/118 (44.07%)			
	Male	Female	Male	Female	
Sex	58/162 (35.80%)	104/162 (64.20%)	1687/3243 (52.02%)	1556 (47.98%)	P<0.001
<i>EGFR</i> SMF*	21/58 (36.21%)	53/104 (50.96%)	689/1687 (40.84%)	1095/1556 (72.30%)	
<i>EGFR</i> SMF	16/58 (27.59%)	47/104 (45.19%)			

*, duplication included. MPLC, multiple primary lung cancer; LUAD, lung adenocarcinoma; SMF, somatic mutation frequencies.

Table S3 Information regarding *EGFR* mutations in 162 MPLC patients

Exon	Type	NT (%)	Sample	Case No.	Sex	NFR	Smoke	Stage
Germline	Total	16 (9.88)						
19	p.746_750del	1	NAT	01	F	1	N	IB
	p.746_750del	1	NAT	02	F	1	N	IA1
19	p.746_751del	1	NAT	03	F	1	N	IB
20	p.S768N	1	NAT	04	F	1	N	IA1
	p.S768I	1	NAT	05	M	2	Y	IA2
	p.S768I	1	NAT	06	F	2	N	IA2
	p.S768I	1	NAT	01	F	1	N	IB
20 ins	p.V769_D770 delins ASV	1	NAT	07	M	2	N	IA1
	p.V769_D770 delins ASV	1	NAT	08	M	2	Y	IA2
20	p.T790M	1	NAT	09	M	3	Y	IIIB
20	p.Q791*	1	NAT	05	M	2	Y	IA2
21	p.V843I(G>A)	1	NAT	10	F	2	N	IB
	L858R	1	NAT	11	F	1	N	IA2
	L858R	1	NAT	12	M	1	N	IB
	L858R	1	NAT	09	M	3	Y	IIIB
	L858R	1	NAT	13	F	1	N	IA2
Somatic	Total	73 (45.06)						
18	C719S	1	Tumor lesion	14	F	1	N	IB
	Total (19)	20 (12.35)						
19del	p.745_750del	1	Tumor lesion	15	F	1	N	IB
	p.745_750del	1	Tumor lesion 1		F	1	N	IA2
			Tumor lesion 2	16				
	p.745_750del	1	Tumor lesion	17	F	1	N	IA2
	p.745_750del	1	Tumor lesion	18	F	1	N	IB
	p.745_750del	1	Tumor lesion	19	M	1	Y	IA1
	p.745_750del	1	Tumor lesion	20	F	1	N	IA2
	p.745_750del	1	Tumor lesion 1		F	2	N	IIB
			Tumor lesion 2	21				
	p.745_750del	1	Tumor lesion	22	F	1	N	IB
	p.746_750del	1	Tumor lesion	23	F	1	N	IIIA
	p.746_750del	1	Tumor lesion 1	2	F	1	N	IA1
			Tumor lesion 2					
	p.746_750del	1	Tumor lesion	24	F	1	N	IB
	p.746_750del	1	Tumor lesion	25	F	1	N	IB
	p.746_750del	1	Tumor lesion 1		F	1	N	IB
			Tumor lesion 2	1				
	p.746_751del	1	Tumor lesion 1		M	1	N	IB
			Tumor lesion 2	3				
	p.747_751del	1	Tumor lesion	26	M	1	Y	IB
	p.747_751del	1	Tumor lesion	27	F	1	N	IIB
	p.747_752del	1	Tumor lesion	28	F	1	N	IA1
	p.747_752del	1	Tumor lesion	29	F	1	N	IB
	p.747_752del	1	Tumor lesion 1		F	1	N	IB
			Tumor lesion 2	30				
	p.751_758del	1	Tumor lesion	31	F	1	N	IA1
	Total (20)	18 (11.11)?						
20ins	p.V769delinsVASV	1	Tumor lesion	32	F	1	N	IB
	p.V769delinsVASV	1	Tumor lesion 1		M	2	N	IA1
			Tumor lesion 2	7				
	p.V769delinsVASV	1	Tumor lesion 1		M	2	Y	IA2
			Tumor lesion 2	8				
	p.V769delinsVASV	1	Tumor lesion 1		F	1	N	IA1
			Tumor lesion 2	4				
	p.D770delinsDSVD	1	Tumor lesion	33	F	1	N	IA1
	p.D770delinsDSVD	1	Tumor lesion 1		F	3	N	IB
			Tumor lesion 2	34				
	p.D770delinsDSVD	1	Tumor lesion	35	F	1	N	IA2
	p.D770delinsDSVD	1	Tumor lesion	36	F	1	N	IB
20	p.S768N	1	Tumor lesion 1		F	1	N	IA1
			Tumor lesion 2	4				
	p.S768I	1	Tumor lesion 1		M	2	Y	IA3
			Tumor lesion 2	5				
	p.S768I	1	Tumor lesion 1		F	2	N	IA2
			Tumor lesion 2	6				
	p.S768I	1	Tumor lesion 1		F	1	N	IB
			Tumor lesion 2	1				
	p.C781Y	1	Tumor lesion	37	M	1	N	IIB
	p.L788V	1	Tumor lesion	20	F	1	N	IA2
	p.T790M	1	Tumor lesion	38	F	1	Y	IA1
	p.T790M	1	Tumor lesion 1		M	3	Y	IIIB
			Tumor lesion 2	9				
	p.T790M	1	Tumor lesion	3	M	1	N	IB
	p.Q791*	1	Tumor lesion	5	M	2	Y	IA3
	Total (21)	34 (20.99)						
21	p.V843I(G>A)	1	Tumor lesion 1		F	2	N	IB
			Tumor lesion 2					
			Tumor lesion 3	10				
	p.V843I(G>A)	1	Tumor lesion	39	M	1	N	IIIA
	p.L858R	1	Tumor lesion	40	M	2	Y	IB
	p.L858R	1	Tumor lesion	41	F	1	N	IA2
	p.L858R	1	Tumor lesion 1		F	1	N	IA2
			Tumor lesion 2	11				
	p.L858R	1	Tumor lesion	42	F	1	N	IB
	p.L858R	1	Tumor lesion	43	F	1	N	IA2
	p.L858R	1	Tumor lesion	44	F	1	N	IA2
	p.L858R	1	Tumor lesion 1		M	1	Y	IB
			Tumor lesion 2	45				
	p.L858R	1	Tumor lesion	46	M	1	N	IB
	p.L858R	1	Tumor lesion 1		M	1	N	IB
			Tumor lesion 2	12				
	p.L858R	1	Tumor lesion	47	F	1	N	IA2
	p.L858R	1	Tumor lesion	48	F	1	N	IB
	p.L858R	1	Tumor lesion	49	F	1	N	IA2
	p.L858R	1	Tumor lesion	50	F	1	N	IA2
	p.L858R	1	Tumor lesion	51	F	1	N	IB
	p.L858R	1	Tumor lesion 1		F	1	N	IA2
			Tumor lesion 2	13				
	p.L858R	1	Tumor lesion	52	F	1	N	IA2
	p.L858R	1	Tumor lesion	53	F	1	N	IA1
	p.L858R	1	Tumor lesion	54	M	1	Y	IA1
	p.L858R	1	Tumor lesion	55	F	1	N	IA1
	p.L858R	1	Tumor lesion	56	F	2	N	IB
	p.L858R	1	Tumor lesion	57	F	1	N	IA2
	p.L858R	1	Tumor lesion	58	M	2	N	IB
	p.L858R	1	Tumor lesion 1		F	1	N	IA2
			Tumor lesion 2	59				
	p.L858R	1	Tumor lesion	60	F	1	Y	IA2
	p.L858R	1	Tumor lesion	61	F	1	N	IB
	p.L858R	1	Tumor lesion	3	M	1	N	IB
	p.L858R	1	Tumor lesion	4	F	2	N	IA1
	p.L858R	1	Tumor lesion 1		M	3	Y	IIIB
			Tumor lesion 2	9				
	p.L858R	1	Tumor lesion	62	M	1	Y	IA3
	p.L858R	1	Tumor lesion	63	F	1	N	IA1
	p.L858R	1	Tumor lesion	24	F	2	N	IB
	p.L858R	1	Tumor lesion	7	M	2	N	IA1

Bold: patients (patient numbers are marked in bold) who have more than one mutation at the same time. NT, number of types; NFR, number of first-order relative lung cancer patients of MPLC patients.

Table S4 Functional prediction of EGFR SNVs by PolyPhen-2 and PROVEAN

Variations	PolyPhen-2		PROVEAN ^a	
	Score	Prediction	Score	Prediction
p. G719A	1.000	Probably damaging	-5.056	Deleterious
p. G719S	1.000	Probably damaging	-5.056	Deleterious
p. G719C	1.000	Probably damaging	-7.584	Deleterious
p. S768I	1.000	Probably damaging	-4.836	Deleterious
p. S768N	1.000	Probably damaging	-2.000	Neutral
p. R776H	1.000	Probably damaging	-4.393	Deleterious
p. R776G	1.000	Probably damaging	-6.148	Deleterious
p. R776C	1.000	Probably damaging	-7.028	Deleterious
p. L788V	1.000	Probably damaging	-2.645	Deleterious
p. T790M	1.000	Probably damaging	-5.292	Deleterious
p. C797S	0.989	Probably damaging	-8.007	Deleterious
p. C781Y	1.000	Probably damaging	-10.360	Deleterious
p. V843I	0.999	Probably damaging	-0.887	Neutral
p. L858Q	1.000	Probably damaging	-5.145	Deleterious
p. L858R	1.000	Probably damaging	-5.202	Deleterious
p. L861Q	0.999	Probably damaging	-5.289	Deleterious
p. L861G	1.000	Probably damaging	-7.073	Deleterious

^a PROVEAN prediction cutoff = -2.5.