

Suppl. Table 13: Positions of tumor-specific methylation sites common between cell lines (≥ 4 out of 5) and primary tumors (≥ 14 out of 18).

chr	start	stop	Ensembl_ID	HGNC.symbol	Description
chr7	97360940	97362189	ENSG00000006128	TAC1	tachykinin, precursor 1
chr20	30639265	30639939	ENSG00000101336	HCK	hemopoietic cell kinase single-minded homolog 1 (Drosophila)
chr6	100911555	100911904	ENSG00000112246	SIM1	neurexophilin 1
chr7	8474326	8475225	ENSG00000122584	NXPH1	neurexophilin 1
chr7	8483076	8483825	ENSG00000122584	NXPH1	neurexophilin 1
chr2	176969205	176970504	ENSG00000128713	HOXD11	homeobox D11
chr1	197879928	197880227	ENSG00000143355	LHX9	LIM homeobox 9 T-cell acute lymphocytic leukemia 1
chr1	47694864	47695213	ENSG00000162367	TAL1	LIM homeobox transcription factor 1, alpha
chr1	165323327	165323876	ENSG00000162761	LMX1A	eomesodermin
chr3	27765097	27765996	ENSG00000163508	EOMES/TBR2	NK6 homeobox 1
chr4	85402627	85403376	ENSG00000163623	NKX6-1	heart and neural crest derivatives expressed 2 zinc finger and BTB domain containing 43 vestigial like 2 (Drosophila)
chr4	174448276	174448725	ENSG00000164107	HAND2	homeobox D4
chr9	129566330	129566679	ENSG00000169155	ZBTB43	kelch-like 6 (Drosophila) regulated endocrine- specific protein 18 homolog (rat)
chr6	117584408	117584857	ENSG00000170162	VGLL2	SRY (sex determining region Y)-box 1
chr2	177027205	177027529	ENSG00000170166	HOXD4	NK2 homeobox 5
chr3	183274057	183274331	ENSG00000172578	KLHL6	chromosome 14 open reading frame 23
chr2	220196257	220197006	ENSG00000182698	RESP18	zinc finger protein 560
chr13	112719950	112720174	ENSG00000182968	SOX1	histone cluster 1, H4i
chr5	172660795	172660844	ENSG00000183072	NKX2-5	microRNA 124-1
chr14	29243250	29243899	ENSG00000186960	C14orf23	Uncharacterized protein interferon, alpha 12, pseudogene
chr19	9608951	9609250	ENSG00000198028	ZNF560	
chr6	27107272	27107346	ENSG00000198339	HIST1H4I	
chr8	9756191	9756540	ENSG00000208010	MIR124-1	
chr4	122685401	122685475	ENSG00000226757		
chr9	21402751	21403100	ENSG00000235108	IFNA12P	
chr2	177004205	177004604	ENSG00000237380		
chr7	129422815	129423514	ENSG00000242078		

Suppl. Table 14: Genes involved in neuronal fate commitment, correlated with hyper-methylation in at least 33% of the tumors.*

Ensembl ID	HGNC symbol	Description
ENSG00000009709	PAX7	paired box 7 [Source:HGNC Symbol;Acc:8621]
ENSG00000129514	FOXA1	forkhead box A1 [Source:HGNC Symbol;Acc:5021]
ENSG00000135903	PAX3	paired box 3 [Source:HGNC Symbol;Acc:8617]
ENSG00000128710	HOXD10	homeobox D10 [Source:HGNC Symbol;Acc:5133]
ENSG00000125820	NKX2-2	NK2 homeobox 2 [Source:HGNC Symbol;Acc:7835]
ENSG00000169840	GSX1	GS homeobox 1 [Source:HGNC Symbol;Acc:20374]
ENSG00000106038	EVX1	even-skipped homeobox 1 [Source:HGNC Symbol;Acc:3506]
ENSG00000205927	OLIG2	oligodendrocyte lineage transcription factor 2 [Source:HGNC Symbol;Acc:9398]
ENSG00000180818	HOXC10	homeobox C10 [Source:HGNC Symbol;Acc:5122]
ENSG00000163623	NKX6-1	NK6 homeobox 1 [Source:HGNC Symbol;Acc:7839]
ENSG00000136352	NKX2-1	NK2 homeobox 1 [Source:HGNC Symbol;Acc:11825]

* Gene IDs were derived by DAVID gene ontology analysis using all gene IDs related to hyper-methylation in at least 33% of the tumors and selecting genes belonging to GO:0048663.

Suppl. Table 15: Homeobox genes methylated at the promoter in 33% or more of primary SCLCs

Ensembl ID	HGNC Symbol	Description
ENSG00000116035	VAX2	ventral anterior homeobox 2 [Source:HGNC Symbol;Acc:12661]
ENSG00000128713	HOXD11	homeobox D11 [Source:HGNC Symbol;Acc:5134]
ENSG00000128714	HOXD13	homeobox D13 [Source:HGNC Symbol;Acc:5136]
ENSG00000091010	POU4F3	POU class 4 homeobox 3 [Source:HGNC Symbol;Acc:9220]
ENSG00000162624	LHX8	LIM homeobox 8 [Source:HGNC Symbol;Acc:28838]
ENSG00000091656	ZFX4	zinc finger homeobox 4 [Source:HGNC Symbol;Acc:30939]
ENSG00000128710	HOXD10	homeobox D10 [Source:HGNC Symbol;Acc:5133]
ENSG00000169840	GSX1	GS homeobox 1 [Source:HGNC Symbol;Acc:20374]
ENSG00000163064	EN1	engrailed homeobox 1 [Source:HGNC Symbol;Acc:3342]
ENSG00000117707	PROX1	prospero homeobox 1 [Source:HGNC Symbol;Acc:9459]
ENSG00000188816	HMX2	H6 family homeobox 2 [Source:HGNC Symbol;Acc:5018]
ENSG00000106038	EVX1	even-skipped homeobox 1 [Source:HGNC Symbol;Acc:3506]
ENSG00000163623	NKX6-1	NK6 homeobox 1 [Source:HGNC Symbol;Acc:7839]
ENSG00000188909	BSX	brain-specific homeobox [Source:HGNC Symbol;Acc:20450]
ENSG00000143418	LASS2	LAG1 homolog, ceramide synthase 2 [Source:HGNC Symbol;Acc:14076]
ENSG00000188620	HMX3	H6 family homeobox 3 [Source:HGNC Symbol;Acc:5019]
ENSG00000172789	AC012531.1	Homeobox protein Hox-C5 [Source:UniProtKB/Swiss-Prot;Acc:Q00444]
ENSG00000119919	NKX2-3	NK2 transcription factor related, locus 3 (Drosophila) [Source:HGNC Symbol;Acc:7836]
ENSG00000005073	HOXA11	homeobox A11 [Source:HGNC Symbol;Acc:5101]
ENSG00000109132	PHOX2B	paired-like homeobox 2b [Source:HGNC Symbol;Acc:9143]
ENSG00000133937	GSC	goosecoid homeobox [Source:HGNC Symbol;Acc:4612]
ENSG00000100987	VSX1	visual system homeobox 1 [Source:HGNC Symbol;Acc:12723]
ENSG00000125820	NKX2-2	NK2 homeobox 2 [Source:HGNC Symbol;Acc:7835]
ENSG00000106511	MEOX2	mesenchyme homeobox 2 [Source:HGNC Symbol;Acc:7014]
ENSG00000113430	IRX4	iroquois homeobox 4 [Source:HGNC Symbol;Acc:6129]
ENSG00000136352	NKX2-1	NK2 homeobox 1 [Source:HGNC Symbol;Acc:11825]
ENSG00000198353	HOXC5	homeobox C5 [Source:HGNC Symbol;Acc:5127]
ENSG00000198353	HOXC5	Homeobox protein Hox-C5 [Source:UniProtKB/Swiss-Prot;Acc:Q00444]
ENSG00000009709	PAX7	paired box 7 [Source:HGNC Symbol;Acc:8621]
ENSG00000135903	PAX3	paired box 3 [Source:HGNC Symbol;Acc:8617]
ENSG00000183072	NKX2-5	NK2 transcription factor related, locus 5 (Drosophila) [Source:HGNC Symbol;Acc:2488]
ENSG00000180053	NKX2-6	NK2 transcription factor related, locus 6 (Drosophila) [Source:HGNC Symbol;Acc:32940]
ENSG00000185155	MIXL1	Mix1 homeobox-like 1 (Xenopus laevis) [Source:HGNC Symbol;Acc:13363]
ENSG00000150051	MKX	mohawk homeobox [Source:HGNC Symbol;Acc:23729]
ENSG00000138083	SIX3	SIX homeobox 3 [Source:HGNC Symbol;Acc:10889]
ENSG00000128709	HOXD9	homeobox D9 [Source:HGNC Symbol;Acc:5140]
ENSG00000169856	ONECUT1	one cut homeobox 1 [Source:HGNC Symbol;Acc:8138]

Suppl. Table 16: Homeobox genes methylated within the gene body of 33% or more of primary SCLCs

Ensemble ID	HGNC symbol	Description
ENSG00000007372	PAX6	paired box 6 [Source:HGNC Symbol;Acc:8620]
ENSG00000119042	SATB2	SATB homeobox 2 [Source:HGNC Symbol;Acc:21637]
ENSG00000128713	HOXD11	homeobox D11 [Source:HGNC Symbol;Acc:5134]
ENSG00000162761	LMX1A	LIM homeobox transcription factor 1, alpha [Source:HGNC Symbol;Acc:6653]
ENSG00000165495	PKNOX2	PBX/knotted 1 homeobox 2 [Source:HGNC Symbol;Acc:16714]
ENSG00000091656	ZFHX4	zinc finger homeobox 4 [Source:HGNC Symbol;Acc:30939]
ENSG00000128710	HOXD10	homeobox D10 [Source:HGNC Symbol;Acc:5133]
ENSG00000163064	EN1	engrailed homeobox 1 [Source:HGNC Symbol;Acc:3342]
ENSG00000169840	GSX1	GS homeobox 1 [Source:HGNC Symbol;Acc:20374]
ENSG00000117707	PROX1	prospero homeobox 1 [Source:HGNC Symbol;Acc:9459]
ENSG00000052850	ALX4	ALX homeobox 4 [Source:HGNC Symbol;Acc:450]
ENSG00000105997	HOXA3	homeobox A3 [Source:HGNC Symbol;Acc:5104]
ENSG00000188909	BSX	brain-specific homeobox [Source:HGNC Symbol;Acc:20450]
ENSG00000188620	HMX3	H6 family homeobox 3 [Source:HGNC Symbol;Acc:5019]
ENSG00000165556	CDX2	caudal type homeobox 2 [Source:HGNC Symbol;Acc:1806]
ENSG00000159184	HOXB13	homeobox B13 [Source:HGNC Symbol;Acc:5112]
ENSG00000119919	NKX2-3	NK2 transcription factor related, locus 3 (Drosophila) [Source:HGNC Symbol;Acc:7836]
ENSG00000197757	HOXC6	homeobox C6 [Source:HGNC Symbol;Acc:5128]
ENSG00000134438	RAX	retina and anterior neural fold homeobox [Source:HGNC Symbol;Acc:18662]
ENSG00000009709	PAX7	paired box 7 [Source:HGNC Symbol;Acc:8621]
ENSG00000165588	OTX2	orthodenticle homeobox 2 [Source:HGNC Symbol;Acc:8522]
ENSG00000183072	NKX2-5	NK2 transcription factor related, locus 5 (Drosophila) [Source:HGNC Symbol;Acc:2488]
ENSG00000170370	EMX2	empty spiracles homeobox 2 [Source:HGNC Symbol;Acc:3341]
ENSG00000164778	EN2	engrailed homeobox 2 [Source:HGNC Symbol;Acc:3343]
ENSG00000164093	PITX2	paired-like homeodomain 2 [Source:HGNC Symbol;Acc:9005]
ENSG00000128709	HOXD9	homeobox D9 [Source:HGNC Symbol;Acc:5140]
ENSG00000169856	ONECUT1	one cut homeobox 1 [Source:HGNC Symbol;Acc:8138]
ENSG00000171540	OTP	orthopedia homeobox [Source:HGNC Symbol;Acc:8518]
ENSG00000016082	ISL1	ISL LIM homeobox 1 [Source:HGNC Symbol;Acc:6132]
ENSG00000143355	LHX9	LIM homeobox 9 [Source:HGNC Symbol;Acc:14222]
ENSG00000136944	LMX1B	LIM homeobox transcription factor 1, beta [Source:HGNC Symbol;Acc:6654]
ENSG00000123364	HOXC13	homeobox C13 [Source:HGNC Symbol;Acc:5125]

Suppl. Table 17: Primers for COBRA and bisulfite sequencing

Gene	Forward Primer	Reverse Primer
GALNTL1	TGTTTTTTGTTTGGAGTGAAGAGTA	CCCAAAACCACACAACCTAATTAATAA
MIR-10A	TTTTGTAGTTGGATGGGGAAG	TCTATCTATAATATAAAAAACCAAATC
MIR-129-2	GGAGATATTTTGGGTTGAAGG	CAAATACTTTTTAAAAATAAAAACTTCC
MIR-196A2	TTTTATTTTTGGTTGATAAATATGA	TTTAAACCCCAAACCTTAAACAATC
MIR-615	ATTGGAGAAGGAATTTTATTTAAT	TTCTAAAACCAAATTTTAATCTATC
MIR-9-3	GAGTTTAAAAGGTAGTTGAGGGTG	ATTTAACTACTTCCAATTCTTTATTCAA
AMBRA1	TTTTTTTTATGTGAGGGAGGTTTA	CACAAAACCAAACCCAAACTAC
HOXD10	ATTTGGAGGTTTTTAGAGTTGAGATT	CACATAACAACCAAACCAATAAAATT
PROX1	GTATTTTATAGTAGGTTGAGAGGG	CTAAATCTAACAAAAACTCCAACCC
ZNF672	GTGGGGTTAGTTTTTAGTTATATT	CTCTTAAAACAATATTCCCAAC
DMRTA2	TTGTTTTTGATTGTGTAATGGGTAG	CCTTAACCTCAACTCCAAACTATCA