

**Supplementary Table 1.** The sequence of four guide RNAs (sg143-146) are shown.

<b>sg143</b>	<b>Targeting Exon 1</b>	GGCCTTGGAGAGGATCCAAC
<b>sg144</b>		ACACTCGGCACTGGAGCGAG
<b>sg145</b>	<b>Targeting Exon 2</b>	TCTCCAAGGCCCATCTACC
<b>sg146</b>		CGCTCCAGTGCCGAGTGTG

**Supplementary Table 2.** The primer sequences used for detection of 519 bp deletion from Nr2e3 gene.

<b>Nr2e3 (F)</b>	CAAGCAGGCTACCCTTAGGAC
<b>Nr2e3 (R)</b>	TCTCCGCTTTCCTGAACG

**Supplementary Table 3.** Top ten off target sequences by sgRNA 143, 144, 145 and 146

SgRNA	Target sequence	Off-Target sequence	No. of Mismatches	Off target score (MIT)	Off target score (CFD)	Chr No.	Start	End	Strand	Gene affected
sg143	GGCCTTGGA GAGGATCCA ACAGG	TGCCTTTCAGA GGATCCA ACTGG	3	1.737	0.352	chr19	56218 142	56218 164	-	intergenic:Tcf7l2-Gm22271
	GGCCTTGGA GAGGATCCA ACAGG	AGCTTTGGAGG GGATCCA ACTGG	3	1.562	0.468	chr7	25047 295	25047 317	+	intron:Grik5
	GGCCTTGGA GAGGATCCA ACAGG	GGCTGTGTACA GGATCCA AACC	4	1.257	0.128	chr8	25823 667	25823 689	+	intron:Ash2l
	GGCCTTGGA GAGGATCCA ACAGG	GCCTTTCAAA GGATCCA AACAG	4	0.859	0.227	chr11	27750 219	27750 241	-	intergenic:Gm3810-Gm12079
sg144	AACTCGGC ACTGGAGCG AGGGG	AAACTCGGCAC TGGAGCGAGGG G	1	100.00 0	0.727	chr15	35733 608	35733 630	-	intron:Vps13b
	AACTCGGC ACTGGAGCG AGGGG	ACACGCAGCAG TGGAGCGAGGG G	3	0.964	0.160	chr4	82890 82	82891 04	-	intergenic:Car8-Gm11810
	AACTCGGC ACTGGAGCG AGGGG	ACAACTTCACT GGAGCGAGGG G	4	0.891	0.150	chr14	25647 666	25647 688	-	exon:Zmiz1
	AACTCGGC ACTGGAGCG AGGGG	GCACTCAGCAC TGGAGTGTAGT G	3	0.881	0.467	chr8	94842 490	94842 512	+	intergenic:Ciapi1/Coq9-Coq9
sg145	TCTCCAAGG CCCCATCTA CCTGG	TCTCCAGGGCC ACATCTACCTG G	2	2.128	0.504	chr13	49255 151	49255 173	+	intergenic:Susd3-Fgd3
	TCTCCAAGG CCCCATCTA CCTGG	TGTCCAAAGCC CCATCTACTAG G	3	1.492	0.209	chr1	65572 910	65572 932	+	intergenic:Gm8805-Crygf
	TCTCCAAGG CCCCATCTA CCTGG	CCTCCAAGGCC CCATCAACCAG A	2	1.180	0.032	chr3	88075 314	88075 336	-	exon:Ttc24
	TCTCCAAGG CCCCATCTA CCTGG	TCTCACAGACC CATCTACCTGG	4	0.859	0.303	chr18	42749 124	42749 146	-	intron:Ppp2r2b
sg146	CGCTCCAGT GCCGAGTGT GTGGG	CACTTCAGTGC CAAGTGTGTGG G	3	1.089	0.497	chr18	31448 533	31448 555	-	exon:Gm26658/Syt4
	CGCTCCAGT GCCGAGTGT GTGGG	CTCTCCAGTCC CAAGTGTGTGG G	3	1.003	0.235	chr7	13357 6523	13357 6545	-	intergenic:Ctbp2-Tex36
	CGCTCCAGT GCCGAGTGT GTGGG	CTATCCAATGCT GAGTGTGTAGG	4	0.694	0.297	chr14	54071 947	54071 969	+	intergenic:Trdv2-2-Trdv4
	CGCTCCAGT GCCGAGTGT GTGGG	CAGGCCAGTGC AGAGTGTGTGG G	4	0.694	0.189	chr16	86673 96	86674 18	+	intron:Carhsp1

**Supplementary Table 5.** Targeted mouse or human gene specific ChIP primer sequences

ChIP Primers		Sequences 5'-3'
mouse Dino (-213 ~ +63)	Forward	CGCTGCGTGACAAGAGAATA
	Reverse	TGTCTGGATATCGCTGTGGA
mouse Dino (-1808 ~ -1521)	Forward	CTCTTGTGCCGTCTCTGACA
	Reverse	GGAAAAGCATCTTGGAGCTG
mouse Dino (+1377 ~ +1559)	Forward	GATTGTGGCTAAACCCCAAG
	Reverse	CTTCAAGGCAGTGGGAGAAG
mouse Bax (-952 ~ -757)	Forward	AGTGCAGGTTGGTTTTGAGC
	Reverse	GATGCCAGAGTTGGTTGTT
mouse Bak1(-284 ~ -36)	Forward	GAAAGCGGGTAGAGGGGTAG
	Reverse	CTGCAGGGACTGATCTCAAA
Human DINO (-692 ~ -497)	Forward	TACTCCACTCCGCTTTCCCTC
	Reverse	TACAGGAATCCCTGGTCACG

**Supplementary Table 6.** ChIP-grade antibodies used for ChIP assay. The amount used for each ChIP reaction and supplier information were shown.

ChIP-Grade Antibody	Supplier	Catalogue # (Clone)	Amount per reaction
NR2E3	Santa Cruz Biotech, Inc.	sc-292264	3 µg
NR2E3	Aviva Systems Biology	ARP39069	3 µg
Sp1	Active Motif	39058	3 µg
H4Ac	Active Motif	39243	3 µg
H3K4me3	Active Motif	39159	5 µg
H3K4me2	Active Motif	39141	5 µg
LSD1	Active Motif	39186	5 µg
LSD1	Cell Signaling Technology	2139	3 µg
H3K9me3	EpiGentek Group, Inc.	A-4036	3 µg
RNA pol II	EpiGentek Group, Inc.	A-2032	3 µg
p53	Cell Signaling Technology	2524 (1C12)	3 µg

**Supplementary Table 7.** The primer sequences used in chromatin accessibility assay.

Chromatin accessibility Primers		Sequences 5'-3'
mouse Dino ChAc I(-1475 ~ -1290)	Forward	ACCAGGCTGGATCGTGTAAC
	Reverse	TTGGGGTCTTTTGAGACGAG
mouse Dino ChAc II (-356 ~ -105)	Forward	CCCGAAACCCAGGATTTTAT
	Reverse	CCTCCCCTCTGGGAATCTAA
mouse Dino ChAc III (+1232 ~ +1384)	Forward	CCACACCCAGTGTAGGAAGG
	Reverse	ACGTAGGGGACAGAGGAAGC
Human DINO ChAc (-653 ~ -496)	Forward	TACTCCACTCCGCTTTCCCTC
	Reverse	TACAGGAATCCCTGGTCACG

**Supplementary Table 8.** Targeted mouse or human gene specific primer sequences

Primers		Sequences 5'-3'
mouse Nrf2	Forward	CTTTAGTCAGCGACAGAAGGAC
	Reverse	AGGCATCTTGTTTGGGAATGTG
mouse Trp53	Forward	CTCTCCCCCGCAAAGAAAAA
	Reverse	CGGAACATCTCGAAGCGTTTA
mouse Cyp2e1	Forward	CGTTGCCTTGCTTGTCTGGA
	Reverse	AAGAAAGGAATTGGGAAAGGTCC
mouse Gclc	Forward	GGGGTGACGAGGTGGAGTA
	Reverse	GTTGGGGTTTGTCTCTCCC
mouse mdm2	Forward	TGTCTGTGTCTACCGAGGGTG
	Reverse	TCCAACGGACTTTAACAACTTCA
mouse GAPDH	Forward	GCACAGTCAAGGCCGAGAAT
	Reverse	GCCTTCTCCATGGTGGTGAA
mouse Heme oxygenase 1 (Hmox1)	Forward	AGGTACACATCCAAGCCGAGA
	Reverse	CATCACCAGCTTAAAGCCTTCT
mouse p21	Forward	CCTGGTGATGTCCGACCTG
	Reverse	CCATGAGCGCATCGCAATC
mouse Bax	Forward	AGACAGGGGCCTTTTTGCTAC
	Reverse	AATTCGCCGGAGACACTCG
mouse Bak1	Forward	CAGCTTGCTCTCATCGGAGAT
	Reverse	GGTGAAGAGTTCGTAGGCATTC
Human p53	Forward	CCGCAGTCAGATCCTAGCG
	Reverse	AATCATCCATTGCTTGGGACG

**Supplementary Table 9.** Antibodies used for immunoblotting. Optimized incubation buffer, concentration, and supplier information were shown.

Antibody	Supplier	Catalogue # (Clone)	Dilution	Incubation solution
NR2E3	Aviva Systems Biology	ARP39069	1/1000	TBST (0.05%) and 5% milk
ESR1	Santa Cruz Biotech, Inc.	sc-543	1/1000	TBST (0.05%) and 5% milk
AHR	Santa Cruz Biotech, Inc.	sc-133088	1/1000	TBST (0.05%) and 5% milk
Actin	Santa Cruz Biotech, Inc.	sc-1616	1/1000	TBST (0.05%) and 5% milk
Gclc	Proteintech	12601-1-AP	1/1000	TBST (0.05%) and 5% milk
Ho-1	Proteintech	10701-1-AP	1/1000	TBST (0.05%) and 5% milk
p53	Proteintech	10442-1-AP	1/1000	TBST (0.05%) and 5% milk
p53	Santa Cruz Biotech, Inc.	sc-126(DO-1)	1/1000	TBST (0.05%) and 5% milk
p21	Proteintech	60214-1-Ig	1/1000	TBST (0.05%) and 5% milk
Bax	Cell Signaling Technology	14796	1/1000	PBST (0.05%) and 5% milk
Bak1	Cell Signaling Technology	12105	1/1000	PBST (0.05%) and 5% milk
CYP2E1	Enzo Life Sciences, Inc.	BML-CR3271	1/1000	TBST (0.05%) and 5% milk
NRF2	Cell Signaling Technology	12721	1/1000	PBST (0.05%) and 5% milk
pJNK	Cell Signaling Technology	9255	1/1000	PBST (0.05%) and 5% milk
JNK	Cell Signaling Technology	9252	1/1000	PBST (0.05%) and 5% milk