Supplementary Material and Methods

Western blotting - Primary cortical neurons were lysed briefly in homogenizing buffer (1% Triton X-100, 50 mM Tris-HCl, pH 7.5, 0.3 M sucrose, 5 mM EDTA, 2 mM sodium pyrophosphate, 1 mM sodium orthovanadate, 1 mM phenylmethylsulfonyl fluoride (PMSF), 20 μ g/ml leupeptin and 4 μ g/ml aprotinin). Equal amount of the samples was loaded per lane. For detection of Sp1, and tubulin, blots were incubated with antibodies against Sp1 (1:5000, Upstate Biotechnology, Lake Placid, NY) or tubulin (1:5000, Santa Cruz Biotech., Santa Cruz, CA). An enhanced chemiluminescence kit was used for detection. Western blotting was developed in the linear range used for densitometry. The density of the immunoblots was determined by an image analysis system installed with BIO-ID software (Vilber Lourmat, France).

Reporter Assays - Firefly luciferase and Renilla luciferase activities were measured in a luminometer (Model TD 20/20; Turner Designs, Mountain View, CA) using the reagents provided with the dual luciferase reporter kit (Promega, Madison, WI). The assay was carried out following the manufacturer's recommendations. Transfection efficiency and extract preparations were corrected by normalizing the data to the corresponding Renilla luciferase activity for each construct.

 ${}^{35}S$ -Methionine incorporation - At various time points after OGD treatment, cultured cortical neurons with the density of 5 × 10⁵ cells/cm² were washed with PBS and incubated in methionine-free DMEM (Life Technologies-BRL, Rockville, MD), but containing 30 µCi/ml L- ${}^{35}S$ -methionine (New England Nuclear, Boston, MA) for 1 h. *MTS assay* - Primary cortical neurons were plated in 6 × 10⁵ cells/cm² in 24-well plates two days before treatment. Following treatment with shRNA transfection for 30 h, neurons were exposed to OGD challenge. Twenty-four hours later, 20 µl of MTS (5 mg/ml) were added to each well, followed by incubation for an additional 30 min. The media was collected and the absorbance measured at 510 nm using a Rainbow Spectra ELISA microplate reader (TECAN). Cell viability was defined relative to corresponding control cells (i.e. relative cell viability = absorbance of treated sample / absorbance of control sample * 100%).

TUNEL staining - Primary cortical neurons were washed twice in PBS before being fixed 1 hour in 4% paraformaldehyde at 4°C, and permeabilized with 0.1% Triton X-

100 in 1% sodium citrate for 5 min at 4° C. Apoptosis was determined by detecting DNA strand breaks with a TUNEL assay, using the *in situ* death detection kit (Roche Diagnostics GmbH, Mannheim, Germany).

Construction of plasmids - The fragments of rat Sp1 promoter (-1600 to -251) was amplified from normal rat genomic DNA using primers Sp1-F(5'-GGACACCCAGAACAGGTAGGTCTG-3') and Sp1-BglII-R(5'-AGATCTCTCTCTCTGAGGCGTGTA-3'). These PCR product was cloned into plasmid pGL3 vector (Promega, Madison, WI) using the KpnI and BglII restriction sites. The Sp1 5'-UTR (-250 to -1) fragment was amplified from normal rat genomic

DNA using primers Sp1-5'UTR-SpeI-F (5'-ACTAGTAGCGAGTCTTGCCATTGG-3') and Sp1-5'-UTR-EcoRI-R (5'-GGCGCCGGTGGCAGCTGAGGGGGCG-3'). The PCR product was cloned into the pRF or pStemRF vector digested by SpeI and EcoRI restriction sites and named as pRsp1F or pStemRsp1F. Bicistronic reporter plasmids pRF and pStemRF were generous gift of J. T. Tseng (National Cheng-Kung University, Taiwan).

Reverse transcription-PCR and real-time PCR analysis - Primary neurons were mixed with 600 µl of TRI reagent (Invitrogen, Carlsbad, CA) to extract cellular mRNA. Single-strand cDNA was synthesized from the cellular mRNA by adding 1 µl of StrataScriptTM reverse transcriptase (200 U/µl, Stratagene, La Jolla, CA), 10 µl of buffer (250 mM Tris-HCl, 375 mM KCl, and 15 mM MgCl₂), 5 µl of DTT (0.1 M), 1 µl of oligo-dT, and 18 µl of mixed dNTPs (2.5 mM). The mixture was incubated for 50 min at 50°C. The reaction was terminated by heating the mixture to 70°C for 10 min and then icing. Amplification was performed on a thermal cycler (PC800; Astec, Fukuoka, Japan) using DNA polymerase (5 U/µl, Yeastern Biotech). One of the primer sets was added to give a final volume of 20 µl. Reactions were run for the optimal cycles under the following conditions: denaturation at 95°C for 15 sec, annealing at 55°C for 15 sec, and extension at 72°C for 30 sec (repeated for a total of 30 cycles). The primers for the detection of Sp1 cDNA were 5'-

CTGCAAGGGTCTGATTCTCTA-3' and 5'-AGCTTGTCCACCTTGAACTA-3'.

The primers for the detection of GAPDH cDNA were 5'-

TGACAACTTTGGCATCGTGGAAGG-3' and 5'-CAAC

GGATACATTGGGGGTAGGAAC-3'. After PCR amplification, an 8.5 µl aliquot of reaction product was analyzed by electrophoresis on ethidium bromide-stained

agarose gel (1.5 %). Images of the DNA gels after RT-PCR analysis were digitally captured by an image analysis system installed with BIO-ID software (Vilber Lourmat, France). Real-time PCR was carried out with a LightCycler (Roche Diagnostics GmbH, Mannheim, Germany). The primers of HIF-1 α , GAPDH and NR1 were shown in Table 1. The reaction mixture (total volume 10 µl) contained 1 µl of LightCycler DNA Master Hybridization Probes reaction mix (Roche Diagnostics GmbH, Mannheim, Germany), 3 mM MgCl₂, 2 µl of cDNA, 250 nM each of the 2 primers, and 125 nmol/µl each of the dual-labeled fluorescent probes. The primers and the thermal profile were used the same as above. At the end of each annealing step, the fluorescent signal of each reaction was measured at a wavelength of 530 nm with the LightCycler fluorimeter.

RNA interference - To suppress the expression of Sp1, 20 nM Sp1 shRNA (Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan) was transfected to cortical neurons with Lipofectamine 2000 (Invitrogen, Carlsbad, CA). Thirty hours after transfection, neurons were subjected to OGD for various periods of time. At appropriate times, the cells were lysed and assayed for viability or Western blot analyses as described below.

Immunohistochemistry - Indirect labeling methods were used to determine the levels of Sp1 protein in brain tissues. Briefly, rat brain was fixed in 4% paraformaldehyde in PBS for 16 h at 4°C. Transverse slices of 20 µm thickness were cut and the appropriate slices placed on a microscope slide. After a subsequent wash in PBS, slices were permeabilized and blocked for 60 min in 0.1% Triton X-100/5% goat serum/PBS, and incubated for 12 h at 4°C. Brain slices were incubated with rabbit anti-Sp1 antibodies (1:200, Upstate Biotechnology, Lake Placid, NY), anti-MAb1 antibodies (1:50, Chemicon Europe, Hampshire, UK) and mouse anti-NeuN antibody (1:50, Chemicon, Littleton, CO) overnight. After three washes with PBS, cells were incubated with Alexa 488-conjugated anti-rabbit IgG antibodies (1:200, Molecular Probes, Eugene, OR), Alexa 568-conjugated anti-mouse antibodies (1:200, Molecular Probes, Eugene, OR) and DAPI. The slides were washed three times with PBS and mounted with glycerol. Images were analyzed under a confocal fluorescence microscope (Olympus FluoViewTMFV 1000, Melville, NY). Hypoxyprobe (pimonidazole; Chemicon Europe, Hampshire, UK) was intravenously injected into the rat (60 mg/kg) 30 min before MCAO. Animals were sacrificed 45 min after

MCAO and brain tissue was processed for immunohistochemistry.

Supplementary Legends:

Supplementary Videos 1 and 2. - Rats were injected with either saline (Supplementary video 1) or endothelin-1 (ET-1, 240 pmol in 10 μ l of saline over 5 minutes; Supplementary video 2) to the left MCA. Video covers a period of approximately 1 minute.

Supplymentery Fig. 1. Immunohistochemistry for the *in vivo* hypoxia marker pimonidazole - The pitroimidazole was injected intravenously as described in Materials and Methods. A strong signal was shown in the rat ipsilateral brain at 0.45 hr of recovery from MCAO. Contra: Contralateral side; Ipsi: Ipsilateral side.

Supplementary Fig. 2. Genes expression modulated by Sp1 - A, Data obtained from the GEO accession no. GSE63. After filtering, Student's t test was performed. B, The percentage of genes that contained at least one putative Sp1 binding site. The TF-SEARCH program was used to investigate the potential of Sp1 binding site. C, The 'Core Analysis' function included in IPA (Ingenuity System Inc, USA) was used to interpret the data (32 genes) in the context of biological processes. Significance of the biofunctions was tested by the Fisher Exact test p-value. Top ten Diseases and Disorders significantly altered in core analysis. In brackets, number of genes from the input file implicated in each annotation. Significance at p < 0.05.

Supplementary Fig. 3. Sp1 expression in U87 glioma cells and A549 lung cancer cells - The time course of Sp1 expression after OGD treatment in U87 cells (A) or A549 cells (B) was assessed. Total lysates of U87 or A549 cells were obtained at various time points following OGD challenge. Sp1 expression was detected by performing immunoblotting with anti-Sp1 antibodies, using tubulin as an internal control. All experiments were carried out independently in triplicate and were expressed as a percentage of the levels in the naive-controls. Statistical analysis was carried out using the one-way ANOVA with appropriate post hoc tests.

Supplementary Fig. 4. The 5'-flanking region of Sp1 gene was analyzed with Software to predict the IRES-conserved sequence.



Å	4	

Gene Symbol Accession P -value Fold change 1 BC026782 NM_001025575 2.35E-03 1.50 2 Slbp NM_009193 2.59E-02 1.50 3 Hspd1 NM_010477 8.48E-04 1.50 4 Ngo1 NM_008706 3.54E-03 1.51 5 Litaf NM_009890 3.32E-02 1.54 6 Ch25h NM_008928 1.48E-02 1.56 9 Cort NM_013548 2.23E-02 1.56 10 Dnajb3 NM_008299 1.74E-02 1.57 11 Tnfaip8 NM_134131 2.07E-02 1.59 12 Hspa5 NM_002373 4.11E-02 1.62 14 Big1 NM_008973 4.11E-02 1.62 15 Ptn NM_0194470 1.75E-02 1.64 19 Sstr2 NM_0101081 1.15E-02 1.64 21 Ldir NM_0205709 2.8EE-02 1.69 </th <th>68%</th>	68%
1 BC026782 NM_001025575 2.35E-03 1.50 2 Slbp NM_009193 2.59E-02 1.50 3 Hspd1 NM_010477 8.48E-04 1.50 4 Nqol NM_008706 3.54E-03 1.51 5 Litaf NM_00980 3.32E-02 1.54 6 Ch25h NM_008928 1.48E-02 1.56 8 Hist1h3a NM_013548 2.23E-02 1.56 9 Cort NM_007745 4.61E-03 1.56 10 Dnajb3 NM_008299 1.74E-02 1.57 11 Tnfaip8 NM_134131 2.07E-02 1.59 13 Hmgcr NM_0022310 1.29E-02 1.62 14 Btg1 NM_008759 3.162 1.62 15 Ptn NM_010477 1.15E-02 1.64 18 Lrrc6 NM_010477 1.85E-02 1.64 21 Ldir NM_000579 1.81E-02 1.75 25 Mest NM_0025700 2.86E-03 1.79	68%
2 Slbp NM_009193 2.59E-02 1.50 3 Hspd1 NM_010477 8.48E-04 1.50 4 Nqo1 NM_008706 3.54E-03 1.51 5 Litaf NM_019980 5.64E-03 1.54 6 Ch25h NM_009890 3.32E-02 1.54 7 Map2k3 NM_008928 1.48E-02 1.56 8 Hist1h3a NM_013548 2.23E-02 1.56 9 Cort $NM_0008299$ 1.74E-02 1.57 11 Tnfaip8 NM_13131 2.07E-02 1.59 12 Hspa5 NM_008299 1.74E-02 1.59 13 Hmgcr NM_008255 1.30E-02 1.62 14 Btg1 NM_008255 1.30E-02 1.62 14 Btg1 NM_008255 1.30E-02 1.62 15 Ptn NM_008255 1.30E-02 1.62 16 Ligp2 NM_019440 3.78E-03 1.62 17 Wwtr1 NM_133784 4.14E-03 1.63 18 Lrrc6 NM_019457 1.15E-02 1.64 20 Piga NM_011081 1.15E-02 1.64 21 Ldlr NM_009579 1.81E-02 1.75 25 Mest NM_008590 1.19E-04 1.76 26 Pgm1 NM_002570 2.86E-02 1.79 28 Fam107b NM_025626 3.74E-03 1.85 29 Amotl2 NM_019764 1.54E-02 1.88 31 Hsph1 NM_003579 1.14E-02 1.88 32 Thbd NM_00378 1.00E-02 1.92 33 Serpinh1 NM_00378 1.00E-02 1.92 33 Serpinh1 $NM_0013559$ 2.23E-03 1.88 31 Hsph1 $NM_0013559$ 2.23E-03 1.88 32 Thbd NM_00378 1.00E-02 1.92 33 Serpinh1 $NM_0013559$ 2.23E-03 1.88 31 Hsph1 $NM_0013559$ 2.23E-03 1.88 32 Thbd NM_009378 1.00E-02 1.92 33 Serpinh1 $NM_0013559$ 2.23E-03 1.88 31 Hsph1 $NM_0013559$ 2.23E-03 1.88 32 Thbd NM_009378 1.00E-02 1.92 33 Serpinh1 NM_001359 2.23E-03 1.88 31 Hsph1 NM_001359 2.23E-03 1.88 32 Thbd NM_001359 2.23E-03 1.88 33 Hsph1 NM_001359 2.23E-03 1.88 34 Gjb2 $NM_0011455$ 8.25E-04 2.21 40 50 50 50 50 50 50 50 50 50 5	68%
3 Hspd1 NM_010477 8.48E-04 1.50 4 Nqo1 NM_008706 3.54E-03 1.51 5 Litaf NM_009800 3.32E-02 1.54 6 Ch25h NM_008928 1.48E-02 1.56 8 Hist1h3a NM_013548 2.23E-02 1.56 9 Cort NM_008299 1.74E-02 1.57 11 Tnfaip8 NM_022310 1.29E-02 1.59 12 Hspa5 NM_008255 1.30E-02 1.62 14 Btg1 NM_008573 4.11E-02 1.62 15 Ptn NM_008973 4.11E-02 1.62 16 Ligp2 NM_019457 1.15E-02 1.64 21 Ldlr NM_010700 2.32E-03 1.66 21 Ldlr NM_0029035 3.01E-02 1.69 24 Slc30a1 NM_0025700 2.86E-02 1.79 25 Mest NM_0013692 1.44E-03 1.85 26 Pgm1 NM_025626 3.74E-03 1.85 <tr< td=""><td>68%</td></tr<>	68%
4 Nqo1 NM_008706 $3.54E-03$ 1.51 5 Litaf NM_019980 $5.64E-03$ 1.54 6 Ch25h NM_008928 $1.48E-02$ 1.56 7 Map2k3 NM_008298 $1.48E-02$ 1.56 8 Histh3a NM_013548 $2.23E-02$ 1.56 9 Cort NM_008299 $1.74E-02$ 1.57 11 Tnfaip8 NM_01351 $2.07E-02$ 1.59 12 Hspa5 NM_022310 $1.29E-02$ 1.59 13 Hmgcr NM_008255 $1.30E-02$ 1.62 14 Btg1 NM_007569 $3.51E-03$ 1.62 15 Ptn NM_019457 $1.15E-02$ 1.64 19 Sstr2 NM_001042606 $4.67E-03$ 1.64 21 Ldlr NM_019379 $1.81E-02$ 1.64 21 Ldlr NM_020305 $3.01E-02$ 1.69 24 Slc30a1 NM_025700 $2.86E-02$ 1.79 25 Mest NM_009579	68%
5 Litaf NM_019980 5.64E-03 1.54 6 Ch25h NM_009890 3.32E-02 1.54 7 Map2k3 NM_008928 1.48E-02 1.56 8 Hist1h3a NM_013548 2.23E-02 1.56 9 Cort NM_007745 4.61E-03 1.56 10 Dnajb3 NM_008299 1.74E-02 1.57 11 Tnfaip8 NM_134131 2.07E-02 1.59 12 Hspa5 NM_008299 1.74E-02 1.59 13 Hmgcr NM_008255 1.30E-02 1.62 14 Btg1 NM_007569 3.51E-03 1.62 15 Ptn NM_008973 4.11E-02 1.62 16 ligp2 NM_019440 3.78E-03 1.62 17 Wwtr1 $NM_{13}3784$ 4.14E-03 1.63 18 Lrrc6 NM_019457 1.15E-02 1.64 19 Sstr2 $NM_001042606$ 4.67E-03 1.64 20 Piga NM_011081 1.15E-02 1.64 21 Ldlr NM_009579 1.81E-02 1.67 23 Spsb1 NM_009579 1.81E-02 1.75 25 Mest NM_009579 1.81E-02 1.75 25 Mest NM_009579 1.81E-02 1.75 25 Mest NM_009579 1.81E-02 1.75 25 Mest NM_009579 1.81E-02 1.75 26 Mest NM_009579 1.81E-02 1.79 27 Ndel1 NM_025626 3.74E-03 1.85 29 Amotl2 NM_011642 1.54E-02 1.86 30 Klf10 NM_013692 1.14E-02 1.88 32 Thbd NM_009378 1.00E-02 1.92 33 Serpinh1 NM_00359 1.19E-04 2.02 4 Gjb2 NM_008125 1.48E-03 2.16 5 Dusp1 NM_013642 3.37E-03 2.20 36 Map3k1 $NM_00111045$ 8.25E-04 2.21 (9)	68%
6 Ch25h NM_009890 3.32E-02 1.54 7 Map2k3 NM_008928 1.48E-02 1.56 8 Hist1h3a NM_0113548 2.23E-02 1.56 9 Cort NM_007745 4.61E-03 1.56 10 Dnajb3 NM_008299 1.74E-02 1.57 11 Tnfaip8 NM_121311 2.07E-02 1.59 12 Hspa5 NM_008255 1.30E-02 1.62 14 Btg1 NM_008255 1.30E-02 1.62 15 Ptn NM_019440 3.78E-03 1.62 16 ligp2 NM_019457 1.15E-02 1.64 19 Sstr2 NM_001042606 4.67E-03 1.64 21 Ldlr NM_009579 1.81E-02 1.64 21 Ldlr NM_009570 2.86E-02 1.79 25 Mest NM_002500 2.86E-02 1.79 26 Pgm1 NM_025626 3.74E-03 1.85 26 Pgm1 NM_025626 3.74E-03 1.88	68%
7 Map2k3 NM_008928 1.48E-02 1.56 8 Hist1h3a NM_013548 2.23E-02 1.56 9 Cort NM_007745 4.61E-03 1.56 10 Dnajb3 NM_008299 1.74E-02 1.57 11 Tnfaip8 NM_134131 2.07E-02 1.59 12 Hspa5 NM_022310 1.29E-02 1.59 13 Hmgcr NM_008255 1.30E-02 1.62 14 Btg1 NM_007569 3.51E-03 1.62 15 Ptn NM_008973 4.11E-02 1.62 16 Iigp2 NM_019440 3.78E-03 1.62 17 Wwtr1 NM_133784 4.14E-03 1.63 18 Lrrc6 NM_019457 1.15E-02 1.64 19 Sstr2 NM_001042606 4.67E-03 1.64 20 Piga NM_011081 1.15E-02 1.64 21 Ldlr NM_010700 2.32E-03 1.66 22 Golim4 NM_175193 6.90E-03 1.67 23 Spsb1 NM_029035 3.01E-02 1.69 24 Slc30a1 NM_009579 1.81E-02 1.75 25 Mest NM_008590 1.19E-04 1.76 26 Pgm1 NM_025626 3.74E-03 1.85 29 Amotl2 NM_019764 1.54E-02 1.88 31 Hsph1 NM_013692 1.14E-02 1.88 32 Thbd NM_009378 1.00E-02 1.92 33 Serpinh1 NM_003155 2.23E-03 1.88 32 Thbd NM_009378 1.00E-02 1.92 33 Serpinh1 NM_0131642 3.37E-03 2.20 4 Gjb2 NM_008125 1.48E-03 2.16 35 Dusp1 NM_013642 3.37E-03 2.20 36 Map3k1 NM_017205 9.49E-03 2.21 40 $\frac{10}{29}$	68%
8 Hist1h3a NM_013548 2.23E-02 1.56 9 Cort NM_007745 4.61E-03 1.56 10 Dnajb3 NM_008299 1.74E-02 1.57 11 Tnfaip8 NM_134131 2.07E-02 1.59 12 Hspa5 NM_002310 1.29E-02 1.59 13 Hmgcr NM_00855 1.30E-02 1.62 14 Btg1 NM_008973 4.11E-02 1.62 15 Ptn NM_008973 4.11E-02 1.62 16 Tigp2 NM_019440 3.78E-03 1.62 17 Wwtrl NM_133784 4.14E-03 1.63 18 Lrcc6 NM_01042606 4.67E-03 1.64 20 Piga NM_010700 2.32E-03 1.66 22 Golim4 NM_029035 3.01E-02 1.69 24 SIc30a1 NM_002570 2.86E-02 1.79 25 Mest NM_019764 1.54E-02 1.85 29 Amotl2 NM_013692 1.14E-02 1.88	68%
9 Cort NM_007745 4.61E-03 1.56 10 Dnajb3 NM_008299 1.74E-02 1.57 11 Tnfaip8 NM_134131 2.07E-02 1.59 12 Hspa5 NM_0022310 1.29E-02 1.59 13 Hmgcr NM_008555 1.30E-02 1.62 14 Btg1 NM_008973 4.11E-02 1.62 15 Ptn NM_019440 3.78E-03 1.62 17 Wwtrl NM_133784 4.14E-03 1.63 18 Lrrc6 NM_011481 1.15E-02 1.64 19 Sstr2 NM_0100700 2.32E-03 1.66 20 Piga NM_029035 3.01E-02 1.69 24 Slc30a1 NM_029035 3.01E-02 1.69 24 Slc30a1 NM_025700 2.86E-02 1.79 25 Mest NM_013692 1.4E-02 1.88 31 Hsph1 NM_025666 3.74E-03 1.85 29 Amotl2 NM_013692 1.4E-02 1.88	68%
10 Dnajb3 NM_008299 1.74E-02 1.57 11 Tnfaip8 NM_134131 2.07E-02 1.59 12 Hspa5 NM_008255 1.30E-02 1.62 14 Btg1 NM_008555 1.30E-02 1.62 15 Ptn NM_008973 4.11E-02 1.62 16 ligp2 NM_019440 3.78E-03 1.62 17 Wwtrl NM_133784 4.14E-03 1.63 18 Lrrc6 NM_01042606 4.67E-03 1.64 20 Piga NM_010181 1.15E-02 1.64 21 Ldlr NM_009579 1.81E-02 1.64 22 Golim4 NM_175193 6.90E-03 1.67 23 Spsb1 NM_029035 3.01E-02 1.69 24 Slc30a1 NM_025700 2.86E-02 1.79 25 Mest NM_013692 1.4E-02 1.88 32 Fam107b NM_025666 3.74E-03 1.85 29 Amotl2 NM_013692 1.4E-02 1.88	68%
11 Tnfaip8 NM_134131 2.07E-02 1.59 12 Hspa5 NM_0022310 1.29E-02 1.59 13 Hmgcr NM_008255 1.30E-02 1.62 14 Btg1 NM_007569 3.51E-03 1.62 15 Ptn NM_008973 4.11E-02 1.62 16 Ijgp2 NM_019440 3.78E-03 1.62 17 Wwtr1 NM_133784 4.14E-03 1.63 18 Lrrc6 NM_01042606 4.67E-03 1.64 20 Piga NM_010700 2.32E-03 1.66 21 Ldlr NM_020353 3.01E-02 1.64 22 Golim4 NM_025700 2.86E-02 1.79 25 Mest NM_0025626 3.74E-03 1.85 29 Amotl2 NM_01764 1.54E-02 1.88 32 Thbd NM_00378 1.00E-02 1.92 33 Serpinh1 NM_001111043 1.19E-02 2.02 34 Gjb2 NM_008125 1.48E-03 2.16 <td>68%</td>	68%
12 Hspa5 NM_022310 1.29E-02 1.59 13 Hmgcr NM_008255 1.30E-02 1.62 14 Btg1 NM_008973 4.11E-02 1.62 15 Ptn NM_019440 3.78E-03 1.62 16 ligp2 NM_019440 3.78E-03 1.62 17 Wwtrl NM_013784 4.14E-03 1.63 18 Lrcc6 NM_01042606 4.67E-03 1.64 20 Piga NM_010700 2.32E-03 1.66 21 Ldlr NM_00579 1.81E-02 1.64 21 Ldlr NM_00579 1.81E-02 1.75 25 Mest NM_002503 3.01E-02 1.69 24 Slc30a1 NM_025606 3.74E-03 1.85 25 Mest NM_0025606 3.74E-03 1.85 26 Pgm1 NM_025626 3.74E-03 1.85 30 Klf10 NM_013692 1.4E-02 1.88 31 Hsph1 NM_00111043 1.19E-02 2.02 <tr< td=""><td></td></tr<>	
13 Hmgcr NM_008255 1.30E-02 1.62 14 Btg1 NM_007569 3.51E-03 1.62 15 Ptn NM_008973 4.11E-02 1.62 16 ligp2 NM_019440 3.78E-03 1.62 17 Wwtr1 NM_133784 4.14E-03 1.63 18 Lrrc6 NM_019457 1.15E-02 1.64 19 Sstr2 NM_01042606 4.67E-03 1.64 20 Piga NM_01081 1.15E-02 1.64 21 Ldlr NM_01081 1.15E-02 1.64 22 Golim4 NM_029035 3.01E-02 1.64 23 Spsb1 NM_029035 3.01E-02 1.69 24 Slc30a1 NM_025700 2.86E-02 1.79 25 Mest NM_025626 3.74E-03 1.85 29 Amotl2 NM_013692 1.14E-02 1.88 30 Kif10 NM_00378 1.00E-02 1.92 33 Serpinh1 NM_001111043 1.19E-02 2.02	
14 Btg1 NM_007569 3.51E-03 1.62 15 Ptn NM_008973 4.11E-02 1.62 16 Iigp2 NM_019440 3.78E-03 1.62 17 Wwtr1 NM_133784 4.14E-03 1.63 18 Lrrc6 NM_019457 1.15E-02 1.64 20 Piga NM_011081 1.15E-02 1.64 21 Ldlr NM_010700 2.32E-03 1.66 22 Golim4 NM_029035 3.01E-02 1.69 24 Slc30a1 NM_0029035 3.01E-02 1.69 24 Slc30a1 NM_029035 3.01E-02 1.69 24 Slc30a1 NM_025700 2.86E-02 1.79 25 Mest NM_025626 3.74E-03 1.85 29 Amotl2 NM_019764 1.54E-02 1.86 30 Klf10 NM_0031559 2.23E-03 1.88 32 Thbd NM_00111043 1.19E-02 2.02 33 Serpinh1 NM_0013642 3.37E-03 2.16	
15 Ptn NM_008973 4.11E-02 1.62 16 ligp2 NM_019440 3.78E-03 1.62 17 Wwtrl NM_133784 4.14E-03 1.63 18 Lrrc6 NM_019457 1.15E-02 1.64 19 Sstr2 NM_001042606 4.67E-03 1.64 20 Piga NM_010700 2.32E-03 1.66 21 Ldir NM_0029035 3.01E-02 1.64 23 Spsb1 NM_0029035 3.01E-02 1.69 24 Slc30a1 NM_0025709 1.81E-02 1.75 25 Mest NM_002566 3.74E-03 1.85 29 Amotl2 NM_019764 1.54E-02 1.85 29 Amotl2 NM_013692 1.14E-02 1.88 31 Hsph1 NM_00378 1.00E-02 1.92 33 Serpinh1 NM_013642 3.37E-03 2.02 36 Map3k1 NM_01143 1.19E-02 2.02 36 Map3k1 NM_01143 3.221 10	
16 ligp2 NM_019440 3.78E-03 1.62 17 Wwtr1 NM_133784 4.14E-03 1.63 18 Lrrc6 NM_019457 1.15E-02 1.64 19 Sstr2 NM_001042606 4.67E-03 1.64 20 Piga NM_011081 1.15E-02 1.64 21 Ldlr NM_010700 2.32E-03 1.66 22 Golim4 NM_029035 3.01E-02 1.69 24 Slc30a1 NM_009579 1.81E-02 1.75 25 Mest NM_002500 2.86E-02 1.79 24 Slc30a1 NM_025668 7.80E-03 1.67 25 Mest NM_019564 1.54E-02 1.85 29 Amotl2 NM_019692 1.14E-02 1.88 31 Hsph1 NM_00378 1.00E-02 1.92 33 Serpinh1 NM_001111043 1.19E-02 2.02 36 Map3k1 NM_011945 8.25E-04 2.21 0 36 Map3k1 NM_017205 9.49E-03	No Sp1
17 Wwtr1 NM_133784 4.14E-03 1.63 18 Lrrc6 NM_019457 1.15E-02 1.64 19 Sstr2 NM_001042606 4.67E-03 1.64 C. 20 Piga NM_011081 1.15E-02 1.64 C. 21 Ldlr NM_010700 2.32E-03 1.66 C. 22 Golim4 NM_175193 6.90E-03 1.67 G 23 Spsb1 NM_029035 3.01E-02 1.69 G 24 Slc30a1 NM_029035 3.01E-02 1.75 G G 25 Mest NM_008590 1.19E-04 1.76 G G G 26 Pgm1 NM_025626 3.74E-03 1.85 G G G G 27 Ndel1 NM_013692 1.14E-02 1.88 2 G </td <td></td>	
18 Lrrc6 NM_019457 1.15E-02 1.64 19 Sstr2 NM_001042606 4.67E-03 1.64 20 Piga NM_011081 1.15E-02 1.64 21 Ldlr NM_010700 2.32E-03 1.66 22 Golim4 NM_029035 3.01E-02 1.66 23 Spsb1 NM_009579 1.81E-02 1.75 25 Mest NM_0025700 2.86E-02 1.79 26 Pgm1 NM_025606 3.74E-03 1.85 29 Amotl2 NM_019764 1.54E-02 1.86 30 Klf10 NM_013692 1.14E-02 1.88 31 Hsph1 NM_00378 1.00E-02 1.92 33 Serpinh1 NM_001111043 1.19E-02 2.02 34 Gjb2 NM_001812 1.48E-03 2.16 35 Dusp1 NM_0118642 3.37E-03 2.20 36 Mag3k1 NM_011945 8.25E-04 2.21 37 Phf13 NM 172705 9.49E-03 2.21	🗖 Contai
19 Sstr2 NM_001042606 4.67E-03 1.64 C. 20 Piga NM_011081 1.15E-02 1.64 21 Ldlr NM_010700 2.32E-03 1.66 22 Golim4 NM_0175193 6.90E-03 1.67 23 Spsb1 NM_009579 1.81E-02 1.75 25 Mest NM_008590 1.19E-04 1.76 26 Pgm1 NM_025700 2.86E-02 1.79 27 Ndel1 NM_023668 7.80E-03 1.79 28 Fam107b NM_025626 3.74E-03 1.85 29 Amotl2 NM_013692 1.14E-02 1.88 2 30 Klf10 NM_00378 1.00E-02 1.92 1 33 Serpinh1 NM_001111043 1.19E-02 2.02 0 3.37E-03 2.202 34 Gjb2 NM_0013642 3.37E-03 2.20 0 3.37E-03 2.20 36 Map3k1 NM_017205 9.49E-03 2.21 0 3.99 3.97 3.97E-03	
20 Piga NM_011081 1.15E-02 1.64 21 Ldlr NM_010700 2.32E-03 1.66 22 Golim4 NM_175193 6.90E-03 1.67 23 Spsb1 NM_02035 3.01E-02 1.69 24 Slc30a1 NM_008590 1.19E-04 1.75 25 Mest NM_0025700 2.86E-02 1.79 26 Pgm1 NM_025668 7.80E-03 1.85 29 Amotl2 NM_01764 1.54E-02 1.86 30 Klf10 NM_013692 1.14E-02 1.88 31 Hsph1 NM_00378 1.00E-02 1.92 33 Serpinh1 NM_001111043 1.19E-02 2.02 34 Gjb2 NM_008125 1.48E-03 2.16 35 Dusp1 NM_013642 3.37E-03 2.20 36 Mag3k1 NM_0114945 8.25E-04 2.21 37 Phf13 NM 172705 9.49E-03 2.21	
21 Ldlr NM_010700 2.32E-03 1.66 22 Golim4 NM_175193 6.90E-03 1.67 23 Spsb1 NM_029035 3.01E-02 1.69 24 Slc30a1 NM_009579 1.81E-02 1.75 25 Mest NM_002500 2.86E-02 1.79 26 Pgm1 NM_025668 7.80E-03 1.85 27 Ndel1 NM_025626 3.74E-03 1.85 29 Amotl2 NM_013692 1.14E-02 1.88 30 Klf10 NM_013559 2.23E-03 1.88 31 Hsph1 NM_00378 1.00E-02 1.92 33 Serpinh1 NM_001111043 1.19E-02 2.02 34 Gjb2 NM_008125 1.48E-03 2.16 35 Dusp1 NM_013642 3.37E-03 2.20 36 Map3k1 NM_01145 8.25E-04 2.21 37 Phf13 NM 172705 9.49E-03 2.21	
22 Golim4 NM_175193 6.90E-03 1.67 23 Spsb1 NM_029035 3.01E-02 1.69 24 Slc30a1 NM_009579 1.81E-02 1.75 25 Mest NM_0025700 2.86E-02 1.79 26 Pgm1 NM_025668 7.80E-03 1.79 27 Ndel1 NM_025626 3.74E-03 1.85 29 Amotl2 NM_019764 1.54E-02 1.86 30 Klf10 NM_013692 1.14E-02 1.88 2 31 Hsph1 NM_00378 1.00E-02 1.92 1 33 Serpinh1 NM_001111043 1.19E-02 2.02 0 34 Gjb2 NM_008125 1.48E-03 2.16 0 36 Mag3k1 NM_013642 3.37E-03 2.20 0 3 36 Mag3k1 NM_017205 9.49E-03 2.21 (19) 6	
23 Spsb1 NM_029035 3.01E-02 1.69 6 24 Slc30a1 NM_009579 1.81E-02 1.75 25 Mest NM_008590 1.19E-04 1.76 5 26 Pgm1 NM_025700 2.86E-02 1.79 9 4 27 Ndel1 NM_025626 3.74E-03 1.85 9 3 3.74E-03 1.85 9 3 3 9 4 1.79 9 9 4 3 1.79 9 9 4 3 1.79 9 9 4 3 1.79 9 9 4 3 3 1.79 9 9 4 3 3 1.85 9 3 3 9 Amotl2 NM_019764 1.54E-02 1.88 2 1 3 3 1 1.91 1.4E-02 1.88 2 1 3 3 3 1.00E-02 1.92 1 1 3 3 3 3 1.92 1 0 3 3 3 3 3 <	
24 Slc30a1 NM_009579 1.81E-02 1.75 25 Mest NM_008590 1.19E-04 1.76 26 Pgm1 NM_025700 2.86E-02 1.79 27 Ndel1 NM_025626 3.74E-03 1.85 28 Fam107b NM_0126626 3.74E-02 1.86 29 Amotl2 NM_019764 1.54E-02 1.88 2 30 Klf10 NM_013692 1.14E-02 1.88 2 31 Hsph1 NM_00378 1.00E-02 1.92 1 33 Serpinh1 NM_001111043 1.19E-02 2.02 0 34 Gjb2 NM_008125 1.48E-03 2.16 0 35 Dusp1 NM_013642 3.37E-03 2.20 0 36 36 Mag3k1 NM_011945 8.25E-04 2.21 0 36	
25 Mest NM_008590 1.19E-04 1.76 5 26 Pgm1 NM_025700 2.86E-02 1.79 9 27 Ndel1 NM_025626 3.74E-03 1.85 9 28 Fam107b NM_0126626 3.74E-03 1.85 9 29 Amotl2 NM_019764 1.54E-02 1.86 2 30 Klf10 NM_013692 1.14E-02 1.88 2 31 Hsph1 NM_00378 1.00E-02 1.92 1 33 Serpinh1 NM_001111043 1.19E-02 2.02 0 34 Gjb2 NM_008125 1.48E-03 2.16 0 35 Dusp1 NM_011945 8.25E-04 2.21 0 9 36 Mag3k1 NM_011945 8.25E-04 2.21 0 9 9 37 Phf13 NM 172705 9.49E-03 2.21 (19) 10	
26 Pgm1 NM_025700 2.86E-02 1.79 Image: Constraint of the state of th	-
27 Ndel1 NM_023668 7.80E-03 1.79 \$ </td <td></td>	
28 Fam107b NM_025626 3.74E-03 1.85	
29 Amotl2 NM_019764 1.54E-02 1.86 \$30 \$30 Klf10 NM_013692 1.14E-02 1.88 2 30 Klf10 NM_013692 1.14E-02 1.88 2 31 Hsph1 NM_00378 1.00E-02 1.92 1 33 Serpinh1 NM_001111043 1.19E-02 2.02 0 34 Gjb2 NM_008125 1.48E-03 2.16 0 35 Dusp1 NM_013642 3.37E-03 2.20 0 36 Mag3k1 NM_011205 9.49E-03 2.21 (19) 6	
30 Klf10 NM_013692 1.14E-02 1.88 2 31 Hsph1 NM_013559 2.23E-03 1.88 2 32 Thbd NM_009378 1.00E-02 1.92 1 33 Serpinh1 NM_001111043 1.19E-02 2.02 0 34 Gjb2 NM_008125 1.48E-03 2.16 0 36 Mag3k1 NM_011945 8.25E-04 2.21 0 37 Phf13 NM 172705 9.49E-03 2.21 (19)	
31 Hsph1 NM_013559 2.23E-03 1.88 32 Thbd NM_009378 1.00E-02 1.92 1 33 Serpinh1 NM_001111043 1.19E-02 2.02 0 34 Gjb2 NM_008125 1.48E-03 2.16 0 36 Mag3k1 NM_011945 8.25E-04 2.21 0 37 Phf13 NM 172705 9.49E-03 2.21 (19)	
32 Thbd NM_009378 1.00E-02 1.92 1 33 Serpinh1 NM_001111043 1.19E-02 2.02 0 34 Gjb2 NM_008125 1.48E-03 2.16 0 36 Mag3k1 NM_011945 8.25E-04 2.21 0 37 Phf13 NM 172705 9.49E-03 2.21 (19)	
33 Serpinh1 NM_001111043 1.19E-02 2.02 34 Gjb2 NM_008125 1.48E-03 2.16 35 Dusp1 NM_013642 3.37E-03 2.20 36 Map3k1 NM_011945 8.25E-04 2.21 0 37 Phf13 NM_172705 9.49E-03 2.21 (19)	
34 Gjb2 NM_008125 1.48E-03 2.16 0 35 Dusp1 NM_013642 3.37E-03 2.20 5 36 Map3k1 NM_011945 8.25E-04 2.21 5 37 Phf13 NM_172705 9.49E-03 2.21 (19)	
35 Dusp1 NM_013642 3.37E-03 2.20 20 <td></td>	
36 Map3k1 NM_011945 8.25E-04 2.21 0 8	lers
37 Phf13 NM 172705 9.49E-03 2.21 (19)	ord
	Dis
38 Ier3 NM_133662 7.01E-04 2.29	ne
39 Jun NM_010591 8.62E-04 2.38	Liss
40 Procr NM_011171 9.99E-03 2.61 ₽	le/
41 Hba-a1 NM_008218 4.70E-03 2.67	Ę
42 Nfkbiz NM_030612 7.25E-05 3.17	Jue
43 Socs3 NM_007707 6.79E-03 3.35	_
44 Nr4a1 NM_010444 1.18E-02 3.44 (19)	ē
45 Egr1 NM_007913 1.11E-03 3.68 (16)	<u>ලි</u> (9)
46 Gadd45g NM_011817 1.03E-04 3.97	<u>ලි</u> (9)
47 Tnfaip6 NM_009398 2.31E-03 4.71	<u>8</u> (9)





Sup. Fig.2

Sup. Fig. 3



