

## Supplementary Figure Legends

**Supplementary Figure 1** The structure of CXXC4 protein. The Dvl-interaction motif locates in its C-terminus. The lysine (161) or threonine (162) site was mutated into alanine to explore the effect of these two sites on the function of CXXC4.

**Supplementary Figure 2** The effect of the wild type and mutated CXXC4 on the activity of GSK-3 $\beta$ . The activity of GSK-3 $\beta$  was determined by GSK-3 $\beta$  activity assay Human (Hu) Tau [pS396] ELISA Kit (Life Technologies, USA) according to the manufacturer's instructions.

## Supplementary Table 1 Sequence of oligos

| Primers     |  |
|-------------|--|
| Name        | Sequence   |
| GAPDH       | F: GGAGTCAACGGATTTGGT  |
|             | R: GTGATGGGATTTCATTGAT   |
| CXXC4       | F: CTCATCAACTGTGGCGTCTG  |
|             | R: TTAGTTTGCCCTTCATTCC   |
| Cyclin D1   | F: CCCTCGGTGTCCTACTTCAA  |
|             | R: TGGCATTTTGGAGAGGAAGT  |
| c-myc       | F: GCCTCAGAGTGCATCGAC  |
|             | R: TCCACAGAAACAACATCG  |
| CXXC4 ChIP  | F: TGCCTCCTGTTAGTCATTAGA   |
|             | R: CAATATTCTGCACACCTGTTG   |
| CXXC4 shRNA | Top:ATCCCCTTTCCTCTCCACCTTATCCTTCAAGAGAGGATAAGGTGGA<br>GAGGAAATTTTTC    |
|             | Bottom:TCGAGAAAAATTCCTCTCCACCTTATCCTCTCTTGAAGGATAA<br>GGTGGAGAGGAAAGGG |
| siRNA       |  |
| Name        | Sequence   |
| EZH2        | S: CCAUGUUUACAACUAUCAATT   |
|             | AS: UUGAUAGUUGUAAACAUGGTT  |
| CXXC4       | S: GGGAAUGCAUGAACAAGCUTT   |
|             | AS: AGCUUGUUCAUGCAUUCCTT   |

| Probe     |  |
|-----------|--|
| Name      | Sequence   |
| CXXC4 ISH | ATGCACCACCGAAACGACTCCCAGAGGCTGGGGAA;<br>CAAATTGCCAATCTGGCAGACTGCCCCGAGAATCA;<br>TGCAGGAACCGCAAACGGGACACCAGATCTGCAA |

## Supplementary Table 2 Genes upregulated after EZH2 depletion

| Gene Name   |
|---|
| 1-acylglycerol-3-phosphate O-acyltransferase 4 (lysophosphatidic acid acyltransferase, delta) |
| 3'-phosphoadenosine 5'-phosphosulfate synthase 2  |
| A kinase (PRKA) anchor protein 6  |
| Activating transcription factor 7 interacting protein 2                                       |
| Activin A receptor type II-like 1   |
| Acyl-CoA thioesterase 1   |
| Acyl-CoA thioesterase 12  |
| Acyl-CoA thioesterase 2   |
| ADAM metallopeptidase domain 7  |
| ADAM metallopeptidase with thrombospondin type 1 motif, 15                                    |
| ADAM metallopeptidase with thrombospondin type 1 motif, 9                                     |
| ADAMTS-like 1   |
| Adenomatosis polyposis coli down-regulated 1  |
| Adiponectin, C1Q and collagen domain containing   |
| ADP-ribosylation factor-like 11   |
| Alanine-glyoxylate aminotransferase 2   |
| Alanine-glyoxylate aminotransferase 2-like 1  |
| Angiopoietin-like 1   |
| Ankyrin repeat and SOCS box-containing 12   |
| Aquaporin 2 (collecting duct)   |
| Arachidonate 5-lipoxygenase   |
| Arginine vasopressin receptor 1B  |
| Aspartic peptidase, retroviral-like 1   |
| ATP/GTP binding protein-like 2  |
| ATPase family, AAA domain containing 4  |
| ATP-binding cassette, sub-family A (ABC1), member 13  |
| B cell RAG associated protein   |
| B-cell CLL/lymphoma 2   |
| B-cell CLL/lymphoma 2   |
| Beta-carotene oxygenase 2   |
| Betacellulin  |
| Bone morphogenetic protein 8a   |
| Bone morphogenetic protein receptor, type IB  |

Bradykinin receptor B1  
BRCA1 interacting protein C-terminal helicase 1  
Butyrophilin-like 8  
C1q and tumor necrosis factor related protein 1  
C33.6 unnamed HERV-H protein  
Cadherin 12, type 2 (N-cadherin 2)  
Cadherin 12, type 2 (N-cadherin 2)  
Calcium channel, voltage-dependent, alpha 2/delta subunit 3  
Calcium modulating ligand  
Calcyphosine 2  
Calsequestrin 1 (fast-twitch, skeletal muscle)  
Calsequestrin 2 (cardiac muscle)  
Carbamoyl-phosphate synthetase 1, mitochondrial  
Carbamoyl-phosphate synthetase 1, mitochondrial  
Carbamoyl-phosphate synthetase 1, mitochondrial  
Carbohydrate (N-acetylgalactosamine 4-O) sulfotransferase 9  
Carboxypeptidase M  
Carboxypeptidase M  
Carboxypeptidase X (M14 family), member 2  
Carnosine dipeptidase 1 (metallopeptidase M20 family)  
Casein alpha s1  
Caspase 7, apoptosis-related cysteine peptidase  
Caspase-1 dominant-negative inhibitor pseudo-ICE  
Cat eye syndrome chromosome region, candidate 1  
Cathepsin O  
CD109 molecule  
CD200 molecule  
CD38 molecule  
CD40 molecule, TNF receptor superfamily member 5  
CD44 molecule (Indian blood group)  
CD47 molecule  
CD80 molecule  
CD86 molecule  
CDNA clone IMAGE:4303615  
CDNA clone IMAGE:4819084  
CDNA clone IMAGE:5262521  
CDNA clone IMAGE:5276802  
CDNA FLJ11405 fis, clone HEMBA1000769  
CDNA FLJ31660 fis, clone NT2RI2004410  
CDNA FLJ33709 fis, clone BRAWH2007890  
CDNA FLJ34029 fis, clone FCBBF2003636  
CDNA FLJ34775 fis, clone NT2NE2003315  
CDNA FLJ37631 fis, clone BRCOC2015944  
CDNA FLJ37778 fis, clone BRHIP2026557

CDNA FLJ40938 fis, clone UTERU2007639  
CDNA FLJ41862 fis, clone OCBBF1000254  
CDNA FLJ42857 fis, clone BRHIP2009340  
CDNA FLJ90139 fis, clone HEMBB1001026, highly similar to Transmembrane 9  
superfamily protein member 3 precursor  
Centrosomal protein 135kDa  
Centrosomal protein 27kDa  
Chemokine (C-C motif) ligand 13  
Chemokine (C-C motif) receptor 1  
Chemokine (C-X-C motif) ligand 14  
Chloride channel, calcium activated, family member 3  
Cholesterol 25-hydroxylase  
CKLF-like MARVEL transmembrane domain containing 2  
Clarin 1  
Clone IMAGE:121412 mRNA sequence  
Coiled-coil domain containing 102B  
Coiled-coil domain containing 116  
Coiled-coil domain containing 135  
Coiled-coil domain containing 40  
Coiled-coil domain containing 45  
Coiled-coil domain containing 98  
Collagen, type XXVIII, alpha 1  
Collagen-like tail subunit (single strand of homotrimer) of asymmetric  
acetylcholinesterase  
Complement component 1, r subcomponent  
Contactin 2 (axonal)  
Contactin associated protein-like 5  
Corticotropin releasing hormone receptor 2  
C-type lectin domain family 7, member A  
C-type lectin domain family 7, member A  
CXXC finger 4  
Cysteine rich transmembrane BMP regulator 1 (chordin-like)  
Cystic fibrosis transmembrane conductance regulator (ATP-binding cassette  
sub-family C, member 7)  
Cystic fibrosis transmembrane conductance regulator (ATP-binding cassette  
sub-family C, member 7)  
Cytochrome P450, family 1, subfamily B, polypeptide 1  
Cytochrome P450, family 2, subfamily F, polypeptide 1  
Dachsous 2 (Drosophila)  
Dapper, antagonist of beta-catenin, homolog 3 (*Xenopus laevis*)  
DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, Y-linked  
DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 26B  
Dedicator of cytokinesis 11  
Defensin, alpha 5, Paneth cell-specific

Defensin, beta 126  
Defensin, beta 129  
Deiodinase, iodothyronine, type II  
Diacylglycerol kinase, beta 90kDa  
DIRAS family, GTP-binding RAS-like 3  
Dishevelled associated activator of morphogenesis 2  
DNA damage repair and recombination protein RAD52 pseudogene  
DnaJ (Hsp40) homolog, subfamily C, member 14  
Dynein, axonemal, heavy chain 2  
Dynein, axonemal, heavy chain 7  
EF-hand domain family, member B  
ELKS/RAB6-interacting/CAST family member 2  
EPH receptor A10  
Ephrin-A5  
EST from clone 27306, 5' end  
Estrogen receptor 1  
Estrogen receptor 1  
Family with sequence similarity 150, member B  
Family with sequence similarity 26, member C  
Family with sequence similarity 40, member B  
Family with sequence similarity 5, member C  
Family with sequence similarity 50, member B  
Fas ligand (TNF superfamily, member 6)  
Fc receptor-like 5  
Fibroblast growth factor 12  
Fibroblast growth factor 2 (basic)  
Ficolin (collagen/fibrinogen domain containing) 1  
FLJ45803 protein  
FLYWCH family member 2  
Folate hydrolase (prostate-specific membrane antigen) 1  
Follistatin  
Forkhead box N4  
FRAS1 related extracellular matrix 3  
FRSS1829  
Full length insert cDNA clone ZA79D12  
Full length insert cDNA clone ZD94A03  
FUN14 domain containing 2  
FYN binding protein (FYB-120/130)  
FYN binding protein (FYB-120/130)  
G protein-coupled receptor 132  
G protein-coupled receptor 50  
Gamma-aminobutyric acid (GABA) A receptor, beta 3  
Gamma-aminobutyric acid (GABA) A receptor, delta  
Gamma-aminobutyric acid (GABA) receptor, rho 3

General transcription factor IIA, 1-like  
Glutamate receptor interacting protein 2  
Glutamate-ammonia ligase (glutamine synthetase) domain containing 1  
Glycerophosphodiester phosphodiesterase domain containing 2  
Glycine receptor, alpha 3  
Glycoprotein (transmembrane) nmb  
Glycoprotein M6A  
Glycosylphosphatidylinositol specific phospholipase D1  
Gonadotropin-releasing hormone receptor  
Guanylate binding protein 5  
Hemoglobin, beta  
Hemoglobin, gamma A  
Heparan sulfate (glucosamine) 3-O-sulfotransferase 5  
Heparan sulfate (glucosamine) 3-O-sulfotransferase 5  
Hepatitis A virus cellular receptor 2  
Histone cluster 1, H2aa  
Histone cluster 1, H2ac  
Histone cluster 2, H2be  
Histone deacetylase 9  
Homo sapiens, clone IMAGE:5167766, mRNA  
HOP homeobox  
HSPC074  
HtrA serine peptidase 3  
Hydroxyprostaglandin dehydrogenase 15-(NAD)  
Hydroxysteroid dehydrogenase like 2  
Immunoglobulin superfamily, member 21  
Indoleamine-pyrrole 2,3 dioxygenase  
Influenza virus NS1A binding protein  
Insulin-like growth factor 2 mRNA binding protein 1  
Integrin-binding sialoprotein (bone sialoprotein, bone sialoprotein II)  
Inter-alpha (globulin) inhibitor H3  
Interferon induced transmembrane protein 1 (9-27)  
Interferon, alpha-inducible protein 27  
Interleukin 10  
Interleukin 10 receptor, alpha  
Interleukin 13 receptor, alpha 2  
Interleukin 20 receptor, alpha  
Interleukin 21 receptor  
IQ motif containing F2  
Iroquois homeobox 1  
Jumonji domain containing 2C  
Kelch domain containing 8A  
Kelch repeat and BTB (POZ) domain containing 5  
Keratin 1 (epidermolytic hyperkeratosis)

Keratin 20  
Keratin 35  
Keratin 36  
Keratin 37  
Keratin 77  
Keratin associated protein 13-2  
KIAA1109  
KIAA1377  
Kidney-specific secretory protein of 37 kDa  
Killer cell lectin-like receptor subfamily A, member 1  
Killer cell lectin-like receptor subfamily C, member 4  
Kinase suppressor of ras 2  
Laeverin  
Late cornified envelope 2B  
Late cornified envelope 2C  
Leprecan-like 1  
Leucine rich repeat containing 17  
Leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 2  
LOC723809  
Loricrin  
L-threonine dehydrogenase  
Lymphotoxin alpha (TNF superfamily, member 1)  
Lym7 homolog (mouse)  
Lysine-rich coiled-coil 1  
Lysosomal-associated membrane protein 2  
MAS-related GPR, member X2  
Matrix metalloproteinase 7 (matrilysin, uterine)  
Melanoma antigen family A, 10  
Melanoma antigen family A, 11  
Melanoma antigen family E, 2  
Membrane associated guanylate kinase, WW and PDZ domain containing 2  
Mesoderm development candidate 2  
Metallothionein 4  
Microseminoprotein, beta-  
Microtubule-associated protein 1 light chain 3 gamma  
Microtubule-associated protein tau  
Mitogen-activated protein kinase 8 interacting protein 3  
Monocyte to macrophage differentiation-associated 2  
Muscleblind-like 3 (Drosophila)  
Myelin associated glycoprotein  
Myeloid leukemia factor 1  
Myosin XVA  
NADH dehydrogenase (ubiquinone) Fe-S protein 4, 18kDa (NADH-coenzyme Q

reductase)  
Nascent polypeptide-associated complex alpha subunit  
Natural cytotoxicity triggering receptor 1  
N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 4  
Nephroblastoma overexpressed gene  
Nephronectin  
Neuregulin 1  
Neurexin 1  
Neurexin 3  
Neurocalcin delta  
Neurofilament, medium polypeptide 150kDa  
Neuronal pentraxin II  
Neurotensin  
Neurotrophic tyrosine kinase, receptor, type 2  
NFAT activating protein with ITAM motif 1  
Nitric oxide synthase 2A (inducible, hepatocytes)  
NLR family, CARD domain containing 4  
Nucleosome assembly protein 1-like 2  
Olfactory receptor, family 10, subfamily H, member 1  
Olfactory receptor, family 10, subfamily H, member 3  
Olfactory receptor, family 2, subfamily F, member 1  
Olfactory receptor, family 2, subfamily W, member 3  
Olfactory receptor, family 7, subfamily A, member 17  
Olfactory receptor, family 7, subfamily D, member 4  
Olfactory receptor, family 7, subfamily G, member 3  
Oocyte expressed protein homolog (dog)  
Opioid receptor, kappa 1  
Opsin 1 (cone pigments), short-wave-sensitive  
P antigen family, member 4 (prostate associated)  
P25  
P53-regulated apoptosis-inducing protein 1  
Paraneoplastic antigen MA2  
Parvalbumin  
Patched domain containing 1  
PDZK1 interacting protein 1  
Periphilin 1  
Peroxidasin homolog (Drosophila)  
Peroxisomal biogenesis factor 5-like  
PFTAIRE protein kinase 1  
PFTAIRE protein kinase 1  
PGSF1  
Phosphatase and actin regulator 2  
Phosphatidylinositol-4-phosphate 5-kinase, type I, beta  
Phosphodiesterase 4D, cAMP-specific (phosphodiesterase E3 dunce homolog,



Drosophila)  
Phospholipase A2, group IID  
Phospholipase C, epsilon 1  
Phospholipase C-like 2  
Phosphotyrosine interaction domain containing 1  
Plasminogen  
Platelet-derived growth factor receptor, beta polypeptide  
Poly(A) binding protein, cytoplasmic 1-like 2B  
Potassium channel tetramerisation domain containing 7  
Potassium channel, subfamily K, member 3  
Potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3  
Potassium inwardly-rectifying channel, subfamily J, member 10  
Potassium inwardly-rectifying channel, subfamily J, member 5  
POU class 2 homeobox 1  
PRAME family member 2  
PRO0478 protein  
Progesterone and adiponectin receptor family member VIII  
Proprotein convertase subtilisin/kexin type 2  
Protamine 1  
Protein disulfide isomerase family A, member 2  
Protein phosphatase 1, regulatory (inhibitor) subunit 3C  
Protocadherin 17  
Protocadherin alpha 9  
PTPN13-like, Y-linked 2  
Rac/Cdc42 guanine nucleotide exchange factor (GEF) 6  
Radial spoke head 1 homolog (Chlamydomonas)  
Radical S-adenosyl methionine domain containing 2  
RAN binding protein 17  
RAP2C, member of RAS oncogene family  
RAS guanyl releasing protein 1 (calcium and DAG-regulated)  
Receptor (chemosensory) transporter protein 4  
Reelin  
Regeneration associated muscle protease  
Regulatory factor X, 4 (influences HLA class II expression)  
Repetin  
Retrotransposon gag domain containing 1  
Ribosomal protein L22  
Ribosomal protein S6 kinase, 90kDa, polypeptide 3  
Ring finger protein 125  
Ring finger protein 186  
Scinderin  
Secretoglobin, family 2A, member 1  
Serpine peptidase inhibitor, clade A (alpha-1 antitrypsin), member

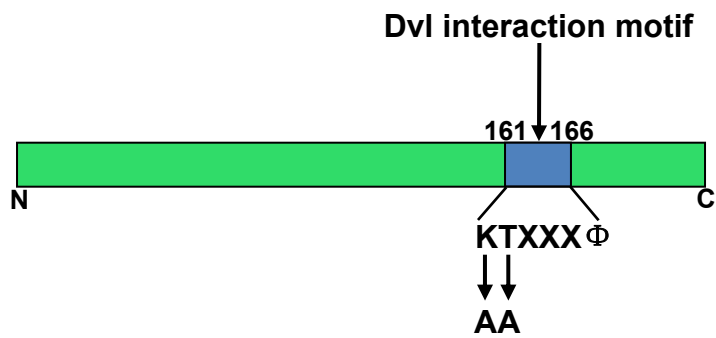
3

Small proline-rich protein 2G  
Sodium channel, voltage-gated, type IV, alpha subunit  
Solute carrier family 12 (sodium/potassium/chloride transporters), member 1  
Solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3  
Solute carrier family 16, member 6 (monocarboxylic acid transporter 7)  
Solute carrier family 24 (sodium/potassium/calcium exchanger), member 1  
Solute carrier family 24 (sodium/potassium/calcium exchanger), member 3  
Solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4  
Solute carrier family 26, member 4  
Solute carrier family 32 (GABA vesicular transporter), member 1  
Solute carrier family 5 (sodium iodide symporter), member 5  
Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4  
Solute carrier family 7 (cationic amino acid transporter, y+ system), member 7  
Solute carrier family 7 (cationic amino acid transporter, y+ system), member 8  
Solute carrier family 7, (neutral amino acid transporter, y+ system) member 10  
Sorting nexin 31  
Sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 3  
Sperm associated antigen 11B  
Sperm associated antigen 8  
Src homology 2 domain containing E  
Starch binding domain 1  
StAR-related lipid transfer (START) domain containing 8  
Sterile alpha motif domain containing 12  
Stomatin (EPB72)-like 3  
Surfactant, pulmonary-associated protein D  
SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2  
Synaptopodin 2  
Synaptotagmin IV  
Synovial sarcoma, X breakpoint 4B  
Syntaxin 4  
Taste receptor, type 2, member 39  
TBC1 domain family, member 9 (with GRAM domain)  
T-cell activation RhoGTPase activating protein  
T-cell leukemia/lymphoma 1A  
Tet oncogene 1  
Thioredoxin domain containing 5  
Thrombospondin, type I, domain containing 7A  
Thymocyte selection-associated high mobility group box  
Tissue factor pathway inhibitor 2  
Transcription elongation factor A (SII), 3  
Transcription elongation factor A (SII)-like 6

Transcription factor AP-4 (activating enhancer binding protein 4)  
Transglutaminase 7  
Transmembrane protease, serine 9  
Transmembrane protein 130  
Transmembrane protein 16C  
Transmembrane protein 178  
Transmembrane protein 31  
Tripartite motif-containing 22  
Tripartite motif-containing 49  
Trophinin  
Tumor necrosis factor (ligand) superfamily, member 10  
Tumor necrosis factor receptor superfamily, member 11b (osteoprotegerin)  
Tumor protein p53 inducible nuclear protein 1  
Tumor protein p53 inducible protein 11  
Tumor protein p63  
Uromodulin-like 1  
Vasoactive intestinal peptide receptor 2  
V-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)  
Versican  
Vitrin  
V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog  
V-myb myeloblastosis viral oncogene homolog (avian)  
V-myc myelocytomatosis viral oncogene homolog 1, lung carcinoma derived (avian)  
V-set and immunoglobulin domain containing 2  
WAP four-disulfide core domain 5  
WD repeat domain 78  
XIAP associated factor 1  
Zic family member 2 (odd-paired homolog, Drosophila)  
Zinc finger and BTB domain containing 32  
Zinc finger CCCH-type containing 13  
Zinc finger protein 135  
Zinc finger protein 169  
Zinc finger protein 382  
Zinc finger protein 41 homolog (mouse)  
Zinc finger protein 432  
Zinc finger protein 445  
Zinc finger protein 568  
Zinc finger protein 608  
Zinc finger protein 616  
Zinc finger protein 99  
Zinc finger, DHHC-type containing 15  
Zinc finger, matrin type 4  
Zinc finger, RAN-binding domain containing 3

ZMYM5  
ZNF451

SFig 1



SFig 2

