

RESEARCH ARTICLE

Open Access



# Messenger RNA profile analysis deciphers new Esrrb responsive genes in prostate cancer cells

Yuan Lu<sup>1,2,5</sup>, Jilong Li<sup>2,3,4</sup>, Jianlin Cheng<sup>2,3,4</sup> and Dennis B. Lubahn<sup>1,2\*</sup>

## Abstract

**Background:** Orphan nuclear receptor estrogen related receptor  $\beta$  (Esrrb or ERR $\beta$ ) is well known in stem cells and early embryonic development. However, little is known about its function in cancer.

**Method:** We investigated the mRNA profile alterations induced by Esrrb expression and its synthetic ligand DY131 in human prostate cancer DU145 cells via RNA-Seq analysis.

**Results:** We distinguished 67 mRNAs differentially expressed by Esrrb alone. Although DY131 alone did not change any gene, treatment of DY131 in the presence of Esrrb altered 1161 mRNAs. These observations indicated Esrrb had both ligand-independent and ligand-dependent activity. When Esrrb was expressed, DY131 treatment further regulated 15 Esrrb-altered mRNAs. DY131 acted as an antagonist for 11 of 15 mRNAs (*wdr52*, *f13a1*, *pxdn*, *spns2*, *loc100506599*, *tagln*, *loc441454*, *tkel1*, *sema3f*, *zcwppw2*, *sdc2*) and as an agonist for 4 of the 15 mRNAs (*rarres3*, *oasl*, *padi2*, *ddx60*). Gene ontology analyses showed altered genes are related to transcription and translation regulation, cell proliferation and apoptosis regulation, and cellular metabolism.

**Conclusion:** Our results characterized mRNA profiles in DU145 prostate cancer cells driven by Esrrb expression and Esrrb ligand DY131, and provided multiple markers to characterize Esrrb's function in Esrrb research.

**Keywords:** Estrogen related receptor, RNA-Seq, Prostate cancer, Gene expression profile, DY131, Transcription regulation, Nuclear receptor

## Background

Esrrb encodes nuclear receptor estrogen related receptor  $\beta$  (Esrrb), which belongs to the nuclear receptor family. Esrrb acts as a transcription factor by binding to a specific DNA sequence estrogen related receptor response element (ERRE), which is also known as steroid factor response element (SFRE), or half site estrogen response element [1, 2].

Esrrb, first cloned in 1988, was not intensively studied until recent years. Knocking out of Esrrb was embryonic lethal due to placental malformation [3]. Though early studies showed a very limited range of tissues with positive Esrrb expression, recent studies reported that short

form Esrrb alternative splicing isoform had a broad range of expression [4]. Esrrb was found to be a core-reprogramming factor to reprogram Pluripotent Stem Cells (iPSCs) [3–6]. *c-myc* and *klf4* of the OSKM (*oct4*, *sox2*, *klf4*, *c-myc*) core-reprogramming factors can be replaced by Esrrb [5, 6]. Esrrb was also recently reported to drive *sox2* transcription and induce iPSC in a single cell system [7].

Tumorigenesis and tumor progression are related to Esrrb. Esrrb was shown to be down-regulated in prostate cancer epithelium compared to normal prostate tissue [8–10]. Its re-expression in DU145 and LNCaP cells was shown to stimulate tumor suppressor *cdkn1a* (p21) concentration. Also, Esrrb can inhibit Estrogen Receptor transcriptional activity in uterine endometrial cancer cells and Nrf2-Keap signaling pathway in breast cancer cells [11, 12].

There are a handful of transcriptome-wide expression survey data from Esrrb knockdown in both human

\*Correspondence: lubahnd@missouri.edu

<sup>1</sup> Department of Biochemistry, University of Missouri, Columbia, MO 65211, USA

Full list of author information is available at the end of the article

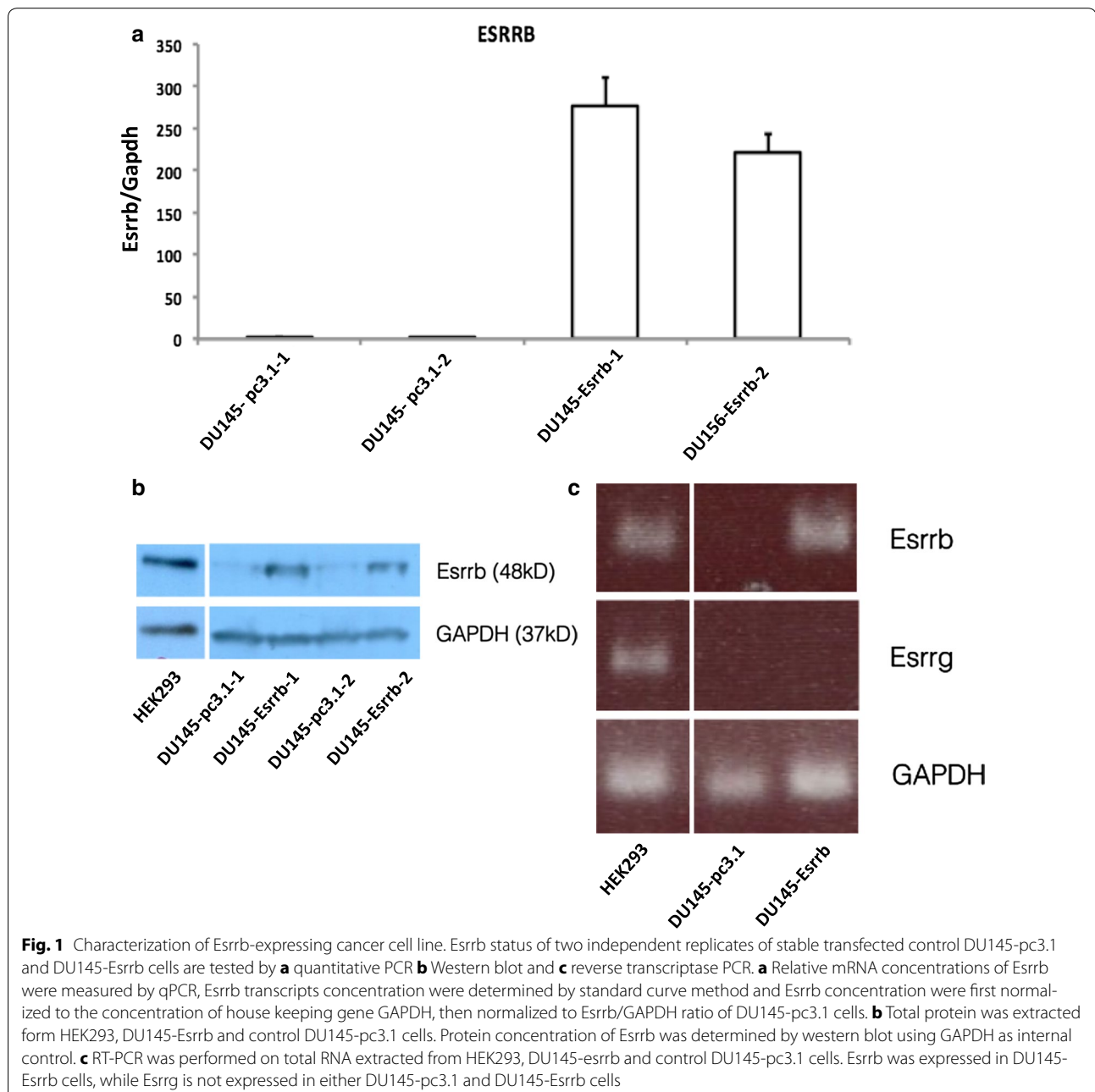
iPSCs and mouse embryonic stem cells [13–16]. Known *Esrrb* controlled genes include *klf4*, *c-myc*, *cdkn1a* and *cyp19a1*, but *Esrrb* target genes in cancer cells are still not known.

This manuscript focuses on the discovery of *Esrrb* ligand-independent and *Esrrb* ligand-dependent target genes. We performed RNA-Seq analysis to characterize *Esrrb* regulated mRNAs in a prostate cancer cell line and we found the treatment of DY131 expanded *Esrrb*'s transcriptional regulation activity to many more genes.

## Results

### Establishment of the *Esrrb* stably transfected DU145 cells

*Esrrb* expression vector or control pcDNA3.1 (Zeo+) vector were transfected into DU145 cells. After 3 weeks of Zeocine selection, we characterized the *Esrrb* status by reverse transcriptase (RT)-PCR, qPCR and western blot analysis (Fig. 1a–c). Our results showed that *Esrrb* was successfully expressed in DU145-*Esrrb* cells. Although RNA-Seq showed that DU145-pc3.1 cells had a very small amount of *Esrrb* expressed (count per



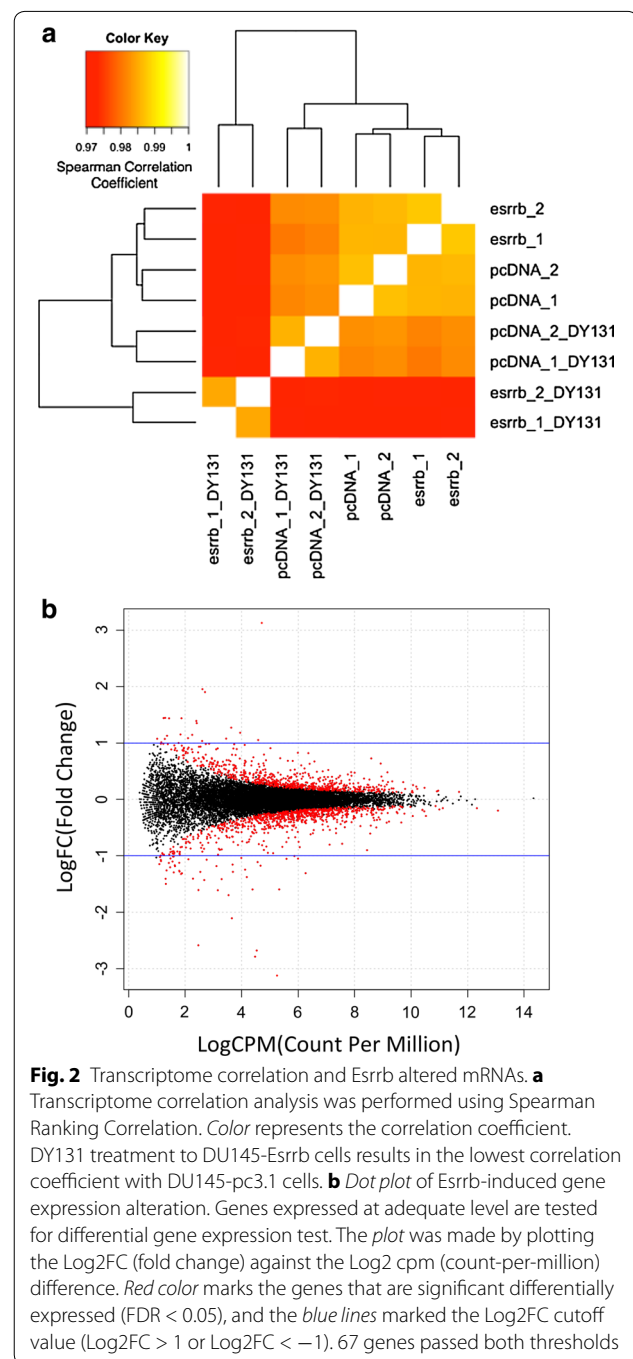
million read <1), the Esrrb concentration is below the detection limit of RT-PCR and western blot. Compared to HEK293 cells, which expressed endogenous Esrrb, overexpression of Esrrb in DU145 cells raised the Esrrb protein concentration to a comparable physiological concentration (Fig. 1b). In addition, our RT-PCR results and RNA-seq results confirmed the estrogen related receptor gamma (Esrrg) was not expressed in DU145 cells. The absence of Esrrg eliminated any possible functional contamination by Esrrg in our Esrrb studies (Fig. 1c).

### Esrrb expression alters mRNA profile

To distinguish genes regulated by Esrrb, we performed RNA-Seq analysis on cDNA libraries constructed from two biological replicates of both DU145-pc3.1 and DU145-Esrrb cells. Spearman ranking correlation analysis showed that the expression of Esrrb in DU145 created a distinct transcriptome compared to control DU145-pc3.1 cells (Fig. 2a). We found 67 genes (21 genes up-regulated, 46 genes down-regulated) altered due to Esrrb expression (Fig. 2b; Table 1). Seven genes that are among the most changed genes (*zcwppw2*, *hoxb8*, *tagln*, *f13a1*, *pxdn*, *aox1*, and *bmp4*, as well as *tgfb* as a negative control) were confirmed by qPCR (Fig. 3). Gene ontology (GO) analysis shows that the products of Esrrb driven differentially expressed genes fell into functional categories of regulation of cell development as well as immune responses (Table 2).

### DY131 requires Esrrb to affect gene expression

To get a more comprehensive understanding of Esrrb-regulated genes and characterize Esrrb's potential ligand dependent activity, control DU145-pc3.1 and DU145-Esrrb cells were treated with Esrrb/Esrrg synthetic ligand DY131. Since both qPCR and RNA-seq show Esrrb transcript concentration is extremely low in DU145 cells and Esrrg is absent, and Esrrb protein concentration is also below the detection limit of western-blot analysis, it was not surprising to observe DY131 treatment without Esrrb expressed did not result in any gene differentially expressed (Fig. 4a). After we applied DY131 to DU145-Esrrb cells, we found DY131 treatment most significantly modified the transcriptome (Figs. 2a, 4b). Further comparison of DU145-Esrrb cells alone to DY131-treated DU145-Esrrb cells detected 1161 altered mRNAs (861 down-regulated, 300 up-regulated). 15 of them overlapped with Esrrb-induced mRNA alterations (Fig. 4c, d; Table 3). We defined an Esrrb agonist as a ligand that moves the mRNA concentration in the direction as Esrrb does; and an antagonist moves the concentration in the opposite direction as Esrrb does. By comparing the trend of the altered genes induced by Esrrb expression and



DY131 treatment, DY131 acts as an agonist for 4 of the 15 genes, and an antagonist for 11 of the 15 genes (Fig. 4d). There are another 1146 mRNAs changed with both Esrrb and DY131 treatment compared to Esrrb alone, indicating their responses is ligand-dependent (Table 3).

GO analysis showed Esrrb-dependent DY131 up-regulated genes were important for regulation of transcription, regulation of apoptosis and proliferation, and a

**Table 1 Esrrb altered mRNAs**

Gene symbol	logFC	P value	FDR
AOX1	-3.49	4.89E-184	3.19E-180
PXDN	-2.79	4.45E-87	1.16E-83
F13A1	-2.68	9.28E-114	4.04E-110
BMP4	-2.59	1.69E-29	1.16E-26
NPTX1	-2.11	1.06E-46	1.73E-43
SPNS2	-1.70	8.70E-31	7.09E-28
DDX60	-1.61	2.43E-15	4.46E-13
NEFL	-1.61	1.84E-13	2.85E-11
OASL	-1.60	1.30E-25	7.07E-23
IFIT3	-1.60	4.29E-42	5.09E-39
WDR52	-1.50	1.85E-06	7.40E-05
C3	-1.43	7.81E-09	5.73E-07
LOC344887	-1.41	5.01E-20	1.49E-17
PCDHB15	-1.41	6.25E-06	0.00020978
CXorf57	-1.41	1.78E-10	1.92E-08
IFI6	-1.38	1.09E-19	2.91E-17
CXCR4	-1.32	3.23E-06	0.00011537
GBP1	-1.31	1.43E-07	7.57E-06
IGFBP3	-1.31	3.19E-89	1.04E-85
ZSCAN12P1	-1.30	0.00015585	0.00302695
RNF128	-1.29	1.58E-10	1.73E-08
SAMD9	-1.29	2.69E-22	1.13E-19
UNC5A	-1.28	8.28E-07	3.62E-05
MX2	-1.27	1.68E-06	6.86E-05
SSBP2	-1.26	5.96E-05	0.00141054
MX1	-1.25	5.99E-22	2.37E-19
SULT4A1	-1.20	4.94E-05	0.00120711
DPYD	-1.19	1.35E-05	0.00040257
NEBL	-1.18	1.16E-12	1.62E-10
TAGLN	-1.18	5.48E-30	3.97E-27
INA	-1.17	2.47E-05	0.0006739
BMF	-1.16	3.32E-05	0.00085559
ESRP1	-1.13	0.00014206	0.00283503
GJA3	-1.12	1.38E-05	0.00040614
IFIT2	-1.11	1.02E-19	2.76E-17
LOC1005065	-1.10	8.53E-05	0.0018618
RARRES3	-1.07	1.84E-07	9.68E-06
TMEM45A	-1.06	4.69E-06	0.00016245
LGALS3BP	-1.05	4.57E-17	9.63E-15
ERAP2	-1.05	1.83E-50	3.41E-47
WNT10A	-1.05	0.00024417	0.00440189
PADI2	-1.04	1.13E-17	2.55E-15
REEP1	-1.01	0.00024704	0.0044413
AMIGO2	-1.01	8.26E-45	1.08E-41
HES1	-0.98	1.30E-07	7.01E-06
FRMD4B	-0.98	0.00014442	0.00284746
NRIP3	0.97	4.28E-14	6.90E-12
HOXB8	0.98	3.60E-11	4.33E-09
KCNQ5	0.98	5.87E-08	3.55E-06

**Table 1 continued**

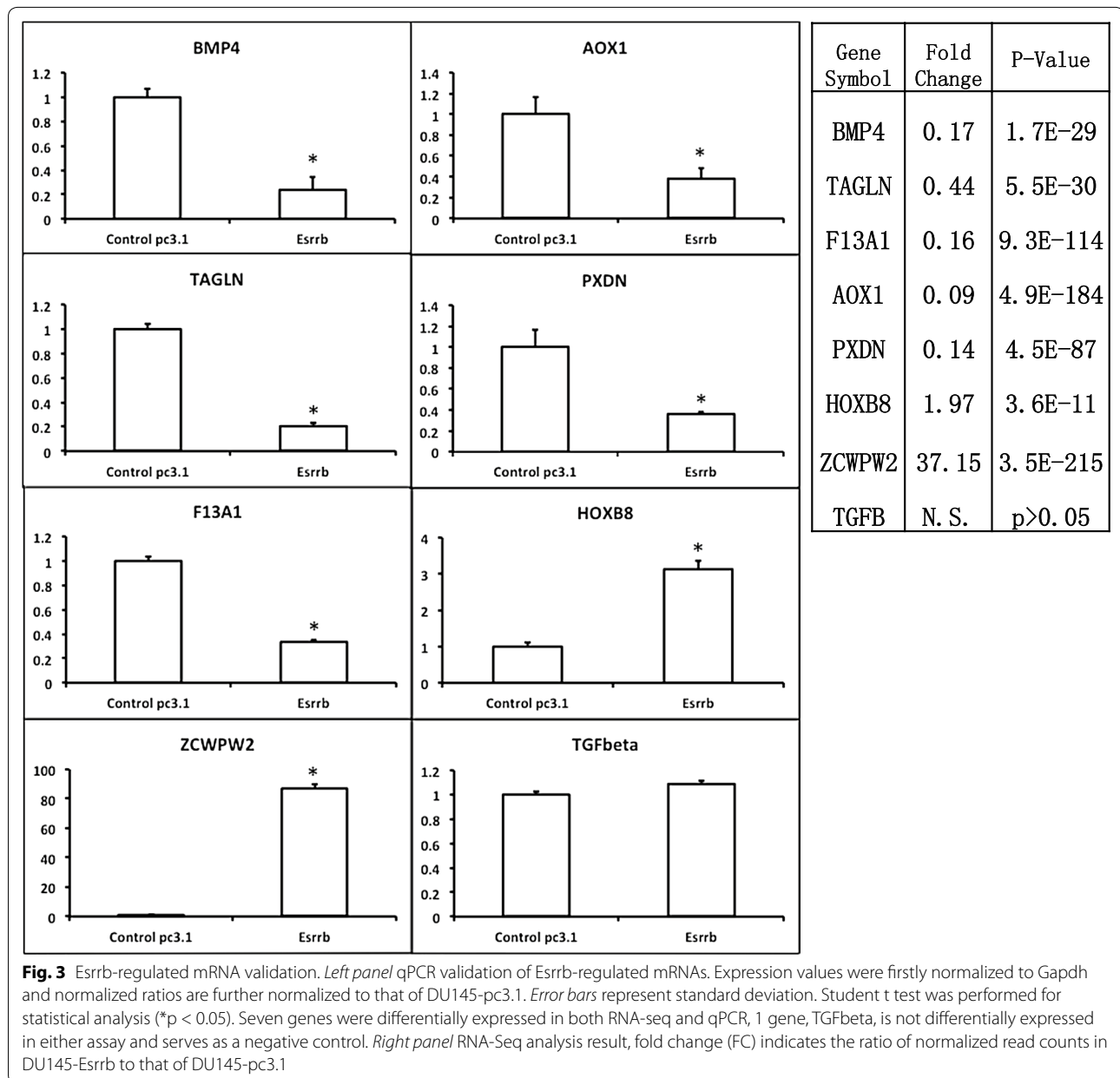
Gene symbol	logFC	P value	FDR
COX6B2	0.99	1.24E-07	6.77E-06
PPFIBP2	1.04	6.38E-07	2.92E-05
KIAA1199	1.06	1.21E-25	6.89E-23
BST1	1.08	4.97E-13	7.30E-11
LOC1001336	1.13	0.00019921	0.00370382
SMOC1	1.15	1.52E-06	6.32E-05
LOC441454	1.15	9.40E-06	0.00029713
DDIT4L	1.18	2.28E-10	2.39E-08
SEMA3F	1.27	2.08E-20	6.96E-18
DUOX1	1.35	5.37E-09	4.25E-07
ARHGAP24	1.39	6.40E-10	6.01E-08
CDHR1	1.44	2.04E-06	7.93E-05
SDC2	1.44	1.49E-08	1.04E-06
SH3RF3	1.44	1.32E-05	0.00039562
PRSS8	1.45	6.96E-06	0.00022989
TKTL1	1.90	3.68E-21	1.33E-18
FGB	1.96	5.57E-22	2.27E-19
ZCWPW2	5.22	3.47E-215	4.53E-211

majority of down-regulated genes are related to oxidation and reduction, metabolism and translation elongation (Table 4; Additional file 1: Table S1).

## Discussion

Esrrb has gained lots of attention in recent years because of its biological function in stem cells and its ability to reprogram somatic cells to iPSC with *oct4* and *sox2* [6, 13, 17–21]. Several other functions of Esrrb have also been discovered including alteration of energy balance, estrogen receptor and glucocorticoid receptor transcription function modulation, Keap1-Nrf2 signaling inhibition, and tumorigenesis in prostate cancer and endometrial adenocarcinoma [9–12, 22–25]. But transcriptome-wide Esrrb function and Esrrb-regulated genes in cancer cells are not well studied.

Esrrb was reported by Chan et al. as a tumor suppressor in DU145 and LNCaP prostate cancer cells using both in vitro and in vivo models [9]. Expression of Esrrb induced *p21/cdkn1a* by directly binding to an ERRE in *p21/cdkn1a*'s promoter, arrested cell cycle at S-phase, and significantly inhibited cell growth [9, 26]. Interestingly, we did not find *p21/cdkn1a* up-regulation after Esrrb expression alone, but after we treated DU145 cells with 3  $\mu$ M DY131, we observed a significant increase of *p21/cdkn1a* mRNA (Table 3; Additional file 2: Figure S1). Scrutinizing the data revealed that Chan's lab cultured their cells with full serum, while we used charcoal-stripped serum for cell culture and DY131 treatment [9].



This implies that there is a compound or factor that can be removed by charcoal treatment modulated Esrrb's activity [27, 28].

From the Esrrb-regulated gene list, we found a few target genes that are related to the known function of Esrrb. *Kiaa1199* encoded gene product has been shown to associate with cellular mortality. A *kiaa1199* mutation was reported to relate to nonsyndromic hearing loss. Considering the significant effect of Esrrb mutations on human hearing loss, *kiaa1199* could be a mediator of Esrrb

mutant related hearing loss [29–32] [33–36]. Another interesting Esrrb responsive gene is *tagln* (Transgelin). It was inhibited by Esrrb while DY131 treatment relieved the inhibition. *Tagln* was reported to promote DU145 cell migration and invasion, indicating Esrrb can also affect DU145 cell behavior by affecting *tagln* [37].

Judging by the numbers of altered genes induced by Esrrb with or without DY131, and the result that DY131 did not alter any mRNA in the absence of Esrrb, we conclude that DY131 activity is Esrrb-dependent.

**Table 2 Gene ontology analysis of *Esrrb* altered mRNAs**

Term	Count	P value
GO:0060284 ~ regulation of cell development	5	0.006
GO:0006955 ~ immune response	8	0.012
GO:0009611 ~ response to wounding	7	0.012
GO:0042542 ~ response to hydrogen peroxide	3	0.017
GO:0050767 ~ regulation of neurogenesis	4	0.022
GO:0006800 ~ oxygen and reactive oxygen species metabolic process	3	0.024
GO:0060052 ~ neurofilament cytoskeleton organization	2	0.029
GO:0000302 ~ response to reactive oxygen species	3	0.03
GO:0051960 ~ regulation of nervous system development	4	0.032
GO:0031960 ~ response to corticosteroid stimulus	3	0.038
GO:0010035 ~ response to inorganic substance	4	0.038
GO:0045661 ~ regulation of myoblast differentiation	2	0.039
GO:0048667 ~ cell morphogenesis involved in neuron differentiation	4	0.04

## Conclusions

In conclusion, we characterized the transcriptome alteration induced by *Esrrb* expression as well as *Esrrb* with its ligand DY131 in prostate cancer cells. We conclude *Esrrb*-target synthetic ligand requires *Esrrb* to generate its gene expression modulation effect. Finally, analysis of *Esrrb* target genes indicates *Esrrb* may be an important factor in regulating cell proliferation.

## Methods

### Cell culture and reagents

DU145 (ATCC Number: HTB-81) and HEK293 (ATCC number: CRL-1571) cells were obtained from the American Type Culture Collection (ATCC). DU145 cells were cultured in RPMI1640 media (Invitrogen, Grand Island, NY, USA) with 10 % Fetal Bovine Serum (FBS) (GE Healthcare Life Sciences, Logan, UT, USA). HEK293 cells were cultured in Eagle's Minimal Essential Medium (DMEM) (Invitrogen, Grand Island, NY, USA) with 10 % FBS. 70 % confluent DU145 cells were transfected with either pcDNA3.1-zeo (+)-*Esrrb* expression vector [4], or control empty vector pcDNA3.1-zeo (+) (Promega, Madison, WI, USA). Empty vector or *Esrrb* expression vector transfected DU145 cells were maintained in medium containing 150 µg/ml Zeocine (Invitrogen, Grand Island, NY, USA) for 3 weeks for selection. Two biological replicates of DU145 cells transfected with *Esrrb* were pooled together respectively and were named DU145-*Esrrb*. Two biological replicates of DU145 cells transfected with control vector were pooled together respectively and were named DU145-pc3.1. Total RNA and protein were collected from cells after they are confluent in 60 mm petri

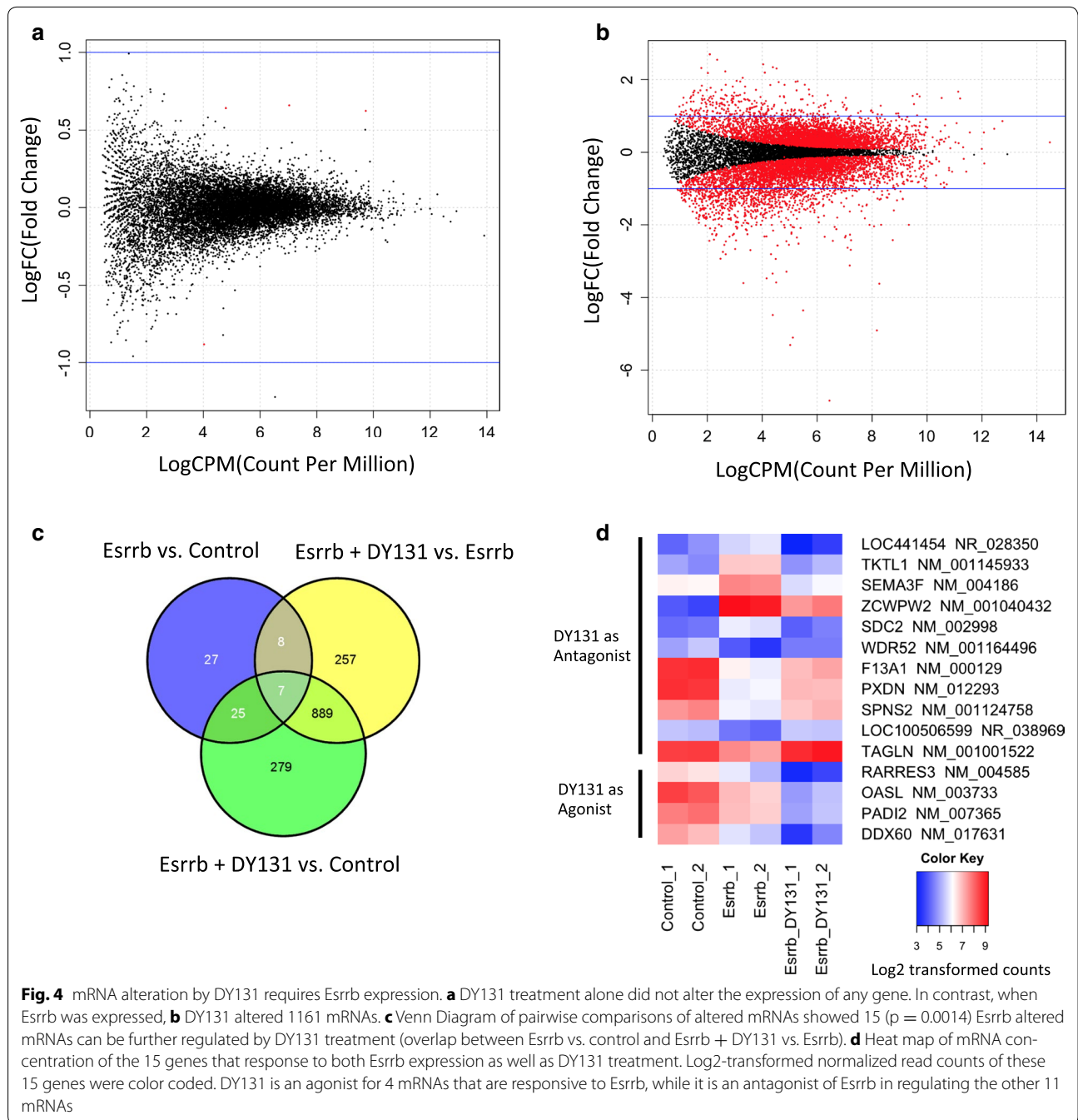
dishes, cultured with phenol-red free RPMI1640 with 10 % Charcoal-stripped FBS [38]. For DY131 (Tocris Bioscience, Bristol, UK) treatment, cells are plated in 60 mm petri dishes until confluent; DU145-pc3.1 and DU145-*Esrrb* are incubated with 3 µM DY131 diluted in medium with charcoal-stripped FBS for indicated length of time.

### Western-blot

Total protein was isolated from DU145-pc3.1, and DU145-*Esrrb* cells. 20 µg protein was loaded on 9 % SDS gels. After the proteins were transferred to nitrocellulose membrane, the membrane was blocked and then incubated with 1:2000 diluted monoclonal anti-*Esrrb* mouse IgG (R&D system, Cat. no: PP-H6705-00) and 1:2000 diluted polyclonal anti-GPADH rabbit IgG (Santa Cruz, Dallas, TX, USA, Cat. no: sc-25777) at 4 degrees overnight. The membrane was then washed and incubated with anti-mouse or anti-rabbit secondary antibody. Chemoluminescence (Promega, Madison, WI, USA) signals were collected using x-ray films (Fisher Scientific, Pittsburg, PA, USA).

### Reverse transcriptase PCR and quantitative PCR

Total RNA was isolated and purified from DU145-pc3.1 and DU145-*Esrrb* using RNeasy kit (Qiagen, Venlo, Netherlands). 1000 ng of total RNA was used to create cDNA libraries using Superscript III Reverse Transcriptase with random primers and oligodT (Invitrogen, Grand Island, NY, USA). *Esrrb* mRNA concentration was determined using quantitative PCR (qPCR) (iQ SYBR, BioRad, Hercules, CA, USA) on ABI7500 system (Applied Biosystems, Foster City, CA, USA). PCR condition: 95°, 30 s; 60°, 40 s; 72°, 40 s. Each qPCR test was performed three times on each of the two biological replicates. Primer sequences: *zcwppw2* (Genbank: NM\_001040432): forward primer: AACAGGGTTGTCTGTGAGACGGA; reverse primer: TGCAGGAGCTTCTGGGCTGC. *hoxb8* (Genbank: NM\_024016): forward primer: GATGCGCCCGCAAGCAGC; reverse primer: CCCAGGGCGT GCGATACCTC. *tagln* (Genbank: NM\_001001522): forward primer: ATGCCCCGGATGACTTGGCT; reverse primer: GCCATGTCTGGGGAAAGCTCCT. *fl3a1* (Genbank: NM\_000129): forward primer: TGTTCGGT GAAATCCGGCCC; reverse primer: TGCACGTCC AG CTCGCCATA. *pxdn* (Genbank: NM\_012293): forward primer: GCAAGCATTAA GGGACTTGCCCT CT; reverse primer: GCAAAAATAGCCTCTCGAGCTT CGG. *aox1* (Genbank: NM\_001159): forward primer: TACGTGAACGGCCGCAAGGT; reverse primer: TGGCTGGGTGATGCCTTATCCT. *bmp4* (Genbank: NM\_001202): forward primer: CCACCACGAAGAA CA TCTGGAG; reverse primer: GCCCTTCCCAAT CAGGGC. *tgfb3*: (Genbank: NM\_000660) forward



primer: AGTGGACATC AACGGGTTAC; reverse primer: CGCACGCAGCAGTTCTTCTC. *gapdh*: (Genbank: NM\_001256799); forward primer: ACCCACT CCTCCACCTTTG; reverse primer: CTCTTGTGCT CTTGCTGGG. *Esrrb*: (Genbank: NM\_004452) forward primer: CAAGAAGCTCAAGGTGGAGAAGGAGGAG; reverse primer: CGGTCTGTCC GTTTGTCTGTCTGTA GGT. *Esrrg*: (Genbank: NM\_001134285) forward primer:

ACCATGAATGGCCATCAGA A; reverse primer: ACC AGCTGAGGGTTCAGGTAT.

**Deep sequencing and differentially expressed genes**

2500 ng total RNA from two biological replicates was used to generate cDNA libraries using TruSeq Stranded mRNA Sample Preparation kits (Illumina, San Diego, CA, USA). RNA quality and fragment sizing of cDNA

**Table 3 DY131 altered mRNAs when Esrrb is expressed**

Gene symbol	logFC	P value	FDR
MTRNR2L8	-6.83	0	0
MTRNR2L10	-5.31	9.85E-242	4.62E-239
SNHG5	-5.11	1.21E-277	6.66E-275
RPS29	-4.91	0	0
SEC61G	-4.48	2.94E-165	7.90E-163
RPL36A	-4.35	2.3501596881585	0.00E+00
RPL12	-3.62	0	0
TMEM212	-3.60	1.12E-56	4.20E-55
ESRG	-3.58	6.76E-114	9.61E-112
NEDD8-MDP1	-3.47	7.24E-102	7.97E-100
FOS	-3.34	2.98E-53	9.94E-52
SLIRP	-3.28	1.01E-127	1.85E-125
MTRNR2L1	-3.12	0	0
LGALS3	-2.94	3.19E-115	4.69E-113
SYTL1	-2.93	9.57E-29	1.23E-27
CLIC3	-2.80	7.42E-29	9.60E-28
WISP2	-2.80	7.36E-56	2.71E-54
ABCD3	-2.74	5.71E-21	4.79E-20
TNNT1	-2.69	4.26E-53	1.42E-51
RPL31	-2.68	0	0
ASS1	-2.66	2.78E-30	3.82E-29
EGR1	-2.63	0	0
PSMA1	-2.57	3.99E-89	3.55E-87
MRPL4	-2.56	5.21E-98	5.36E-96
ACPI	-2.55	8.68E-27	1.02E-25
USMG5	-2.54	4.08E-124	6.97E-122
CRIP1	-2.52	7.63E-155	1.76E-152
STAT4	-2.46	5.11E-22	4.64E-21
NDUFA11	-2.45	2.16E-93	2.05E-91
SCFD1	-2.44	6.21E-304	4.14E-301
CYBA	-2.44	5.78E-17	3.76E-16
NAPSA	-2.43	2.66E-17	1.77E-16
RPL13AP5	-2.43	0	0
RPL9	-2.42	0	0
TCTEX1D2	-2.41	6.26E-19	4.62E-18
MKMK2	-2.35	4.60E-83	3.57E-81
RPL18	-2.35	0	0
MUC1	-2.33	2.97E-73	1.75E-71
SEPP1	-2.33	4.57E-14	2.42E-13
PDE9A	-2.32	1.44E-65	7.05E-64
SEMA6B	-2.32	1.67E-53	5.59E-52
RPS15A	-2.30	0	0
CNTN1	-2.29	3.68E-18	2.58E-17
CA11	-2.28	8.82E-26	9.90E-25
TXN	-2.27	0	0
LOC728730	-2.26	4.28E-15	2.45E-14
GSTM1	-2.26	3.08E-39	6.17E-38
MACROD1	-2.26	5.25E-17	3.42E-16
CBLC	-2.25	5.56E-23	5.30E-22
SUCLG2	-2.24	7.28E-112	9.70E-110
PDCD4	-2.21	4.54E-103	5.13E-101
NDUFB2	-2.16	8.58E-73	4.91E-71
C4orf48	-2.16	1.10E-16	7.00E-16

**Table 3 continued**

Gene symbol	logFC	P value	FDR
PIR-FIGF	-2.15	1.69E-35	2.92E-34
DHRS3	-2.13	4.91E-20	3.92E-19
RPL38	-2.12	4.53E-247	2.20E-244
COX17	-2.11	5.14E-26	5.86E-25
NFE2	-2.10	7.00E-10	2.63E-09
RAB26	-2.09	1.66E-09	6.04E-09
NAPRT1	-2.09	1.48E-116	2.20E-114
CDK5	-2.08	1.31E-28	1.67E-27
NUCB2	-2.08	2.91E-88	2.49E-86
CEBPD	-2.07	5.29E-83	4.08E-81
DYNC2L1	-2.07	5.50E-21	4.63E-20
RPL34	-2.06	6.26E-174	1.88E-171
SNRPF	-2.06	3.85E-103	4.39E-101
BCKDHB	-2.05	9.69E-26	1.09E-24
ANXA1	-2.04	0	0
RARS2	-2.04	4.40E-37	8.15E-36
CYP4F11	-2.04	1.11E-18	8.08E-18
SPC24	-2.03	1.42E-17	9.58E-17
PTP4A3	-2.02	4.47E-19	3.34E-18
LOC728190	-2.02	1.35E-12	6.39E-12
PSME1	-2.01	1.62E-81	1.20E-79
POLE2	-2.00	3.59E-57	1.37E-55
NSMCE4A	-2.00	1.78E-61	7.54E-60
FRA10AC1	-2.00	6.45E-43	1.50E-41
RPS12	-2.00	2.44E-295	1.47E-292
MTRNR2L2	-2.00	4.85E-167	1.33E-164
TYMP	-2.00	1.58E-35	2.74E-34
RPL11	-2.00	0	0
CCDC152	-1.99	6.61E-10	2.49E-09
MXD3	-1.96	3.65E-27	4.38E-26
IL17RC	-1.95	3.51E-23	3.39E-22
GRB7	-1.95	1.64E-32	2.49E-31
LOC441454	-1.94	8.75E-10	3.24E-09
PCCA	-1.94	1.00E-21	8.91E-21
ACBD4	-1.94	2.15E-40	4.51E-39
APLP1	-1.93	7.74E-24	7.77E-23
QARS	-1.93	2.90E-156	6.93E-154
STX8	-1.93	7.69E-26	8.67E-25
TM2D1	-1.92	8.60E-25	9.14E-24
C17orf61	-1.92	1.03E-53	3.49E-52
LOC100507156	-1.91	2.19E-24	2.27E-23
KCNAB2	-1.89	1.65E-43	3.93E-42
CERS4	-1.88	1.66E-27	2.01E-26
C18orf8	-1.86	1.06E-73	6.36E-72
NOTCH3	-1.86	1.46E-16	9.26E-16
LHPP	-1.86	1.93E-12	9.03E-12
GGG7	-1.85	2.37E-13	1.19E-12
RTN2	-1.85	2.10E-09	7.55E-09
SEMA3B	-1.84	2.45E-16	1.52E-15
IL6	-1.84	5.35E-17	3.49E-16
LOC644961	-1.84	1.43E-11	6.24E-11
JPX	-1.83	7.74E-11	3.17E-10
CHCHD6	-1.83	7.00E-19	5.14E-18



**Table 3 continued**

Gene symbol	logFC	P value	FDR
PNPLA6	-1.83	3.33E-86	2.77E-84
FBLN1	-1.82	5.31E-33	8.33E-32
SIDT2	-1.81	5.19E-40	1.07E-38
DEPTOR	-1.81	1.85E-10	7.26E-10
ZNF826P	-1.81	1.25E-08	4.21E-08
TTC39A	-1.81	4.87E-17	3.18E-16
TM7SF2	-1.81	1.91E-67	9.80E-66
ELMO3	-1.81	2.54E-22	2.33E-21
OOEP	-1.81	8.06E-10	3.00E-09
DNAJC17	-1.81	1.40E-14	7.72E-14
TCEA2	-1.80	1.83E-36	3.29E-35
SLC22A18	-1.80	1.89E-19	1.45E-18
ALDH3B1	-1.80	3.28E-68	1.70E-66
LOC100130872	-1.80	6.08E-10	2.30E-09
ETFA	-1.79	1.34E-136	2.74E-134
THYN1	-1.79	9.07E-41	1.92E-39
AKR1C3	-1.78	1.37E-10	5.47E-10
MT1F	-1.78	1.45E-08	4.86E-08
PIP5KL1	-1.78	2.53E-10	9.85E-10
ATP5D	-1.78	1.68E-44	4.13E-43
TMEM120A	-1.77	1.49E-25	1.64E-24
OSBPL5	-1.77	3.00E-09	1.06E-08
TENC1	-1.77	2.65E-18	1.89E-17
EPHX2	-1.76	3.95E-14	2.10E-13
WDR83	-1.76	4.37E-26	4.99E-25
RUVBL2	-1.75	8.63E-147	1.95E-144
KAZALD1	-1.75	6.39E-22	5.77E-21
RPA3	-1.74	6.68E-41	1.42E-39
NOXA1	-1.74	1.23E-09	4.49E-09
TMEM110-MUSTN1	-1.74	5.21E-08	1.65E-07
CACNA2D2	-1.74	8.47E-10	3.14E-09
DICER1-AS1	-1.73	5.04E-10	1.91E-09
ABHD14A-ACY1	-1.73	1.20E-36	2.19E-35
GRAMD2	-1.73	5.14E-08	1.63E-07
PPIH	-1.73	2.97E-19	2.25E-18
STXBP2	-1.73	2.73E-72	1.55E-70
C10orf10	-1.73	3.54E-21	3.02E-20
PLA2G6	-1.73	5.59E-14	2.93E-13
CHEK2	-1.72	1.79E-46	4.82E-45
SPAG4	-1.72	2.30E-15	1.34E-14
COG6	-1.71	9.36E-37	1.71E-35
TBC1D17	-1.71	7.78E-24	7.79E-23
IFT52	-1.71	6.78E-38	1.30E-36
GARNL3	-1.71	7.22E-11	2.96E-10
DLST	-1.70	2.44E-25	2.67E-24
ACSF2	-1.69	3.58E-13	1.77E-12
RYR1	-1.69	4.48E-09	1.57E-08
LOC100134713	-1.68	3.06E-12	1.41E-11
P2RY6	-1.68	7.55E-21	6.27E-20
RARRES3	-1.68	3.75E-07	1.09E-06
C11orf80	-1.67	5.34E-14	2.81E-13
ELF3	-1.67	2.30E-48	6.58E-47
ADCK4	-1.67	2.68E-40	5.60E-39

**Table 3 continued**

Gene symbol	logFC	P value	FDR
GLB1L	-1.67	5.33E-14	2.80E-13
LPPR3	-1.67	1.58E-24	1.66E-23
CDK7	-1.67	1.76E-36	3.16E-35
SLC6A3	-1.66	8.34E-08	2.58E-07
ADAM22	-1.66	2.07E-12	9.64E-12
EIF3K	-1.66	1.65E-98	1.73E-96
S100A4	-1.65	7.75E-10	2.89E-09
ANXA6	-1.65	2.84E-85	2.35E-83
IFT140	-1.65	1.33E-25	1.48E-24
PDIA5	-1.65	1.47E-23	1.44E-22
FADS3	-1.65	2.21E-48	6.32E-47
KCNK15	-1.64	4.58E-21	3.89E-20
FKBP10	-1.64	8.94E-41	1.89E-39
ACSS2	-1.64	1.07E-94	1.06E-92
GSTA4	-1.64	2.80E-31	4.04E-30
KCNMB4	-1.64	8.53E-07	2.38E-06
RPLP2	-1.63	3.48E-220	1.52E-217
UROS	-1.63	2.54E-42	5.73E-41
IFT27	-1.63	4.67E-19	3.49E-18
TRAPP9	-1.63	6.82E-28	8.44E-27
ADAMTSL4	-1.62	5.48E-43	1.28E-41
EIF3E	-1.62	3.34E-248	1.69E-245
ACY1	-1.62	2.83E-30	3.87E-29
MT1X	-1.62	4.27E-24	4.36E-23
LOC643406	-1.61	4.55E-16	2.79E-15
FBXO36	-1.61	1.48E-14	8.12E-14
PACSIN1	-1.61	5.93E-08	1.87E-07
NIT2	-1.61	4.39E-45	1.10E-43
FUZ	-1.60	3.08E-12	1.42E-11
RPL37	-1.60	2.00E-301	1.27E-298
ALDH4A1	-1.60	2.17E-17	1.45E-16
PDCD5	-1.60	6.19E-65	2.92E-63
MFSD3	-1.60	3.51E-31	5.00E-30
EML3	-1.60	1.27E-64	5.92E-63
PSMA3	-1.60	1.93E-96	1.96E-94
TRPT1	-1.59	2.64E-23	2.56E-22
ALDH6A1	-1.59	9.68E-21	8.00E-20
LOC283038	-1.59	3.12E-11	1.32E-10
BDH2	-1.59	1.27E-17	8.59E-17
SDHB	-1.59	1.43E-70	7.78E-69
ARHGFE25	-1.59	1.35E-29	1.79E-28
CYS1	-1.58	4.38E-08	1.40E-07
C8orf45	-1.58	4.42E-08	1.41E-07
GLTSCR2	-1.57	4.94E-46	1.30E-44
JMJD8	-1.57	3.93E-28	4.90E-27
ANKRD24	-1.57	1.17E-07	3.56E-07
SNURF	-1.57	6.25E-68	3.23E-66
SNRPN	-1.57	6.43E-68	3.31E-66
RGN3	-1.57	1.28E-15	7.56E-15
LACTB2	-1.57	2.50E-78	1.75E-76
HSF4	-1.56	1.23E-13	6.27E-13
ENDOV	-1.56	4.24E-09	1.48E-08
CPT1C	-1.55	4.07E-07	1.17E-06

**Table 3 continued**

Gene symbol	logFC	P value	FDR
ITFG1	-1.55	1.10E-88	9.66E-87
IL11RA	-1.55	2.61E-11	1.12E-10
FRG1	-1.55	2.08E-08	6.87E-08
CCDC104	-1.54	8.93E-31	1.25E-29
CERS1	-1.54	4.07E-08	1.30E-07
GDF1	-1.54	4.07E-08	1.30E-07
USP4	-1.54	4.05E-13	2.00E-12
PLCD1	-1.54	6.66E-14	3.47E-13
PBXIP1	-1.54	5.25E-37	9.70E-36
NDUFC1	-1.54	1.61E-42	3.66E-41
CEP70	-1.54	5.71E-59	2.29E-57
MFSD4	-1.54	2.40E-07	7.10E-07
ARPC4-TTLL3	-1.53	3.34E-25	3.64E-24
XRCC1	-1.53	7.89E-35	1.33E-33
CLDN4	-1.52	2.47E-20	2.00E-19
VWA5A	-1.52	7.77E-10	2.90E-09
PC	-1.52	1.73E-20	1.41E-19
MMP11	-1.52	1.58E-09	5.74E-09
C9orf84	-1.52	1.04E-28	1.33E-27
SLC37A2	-1.52	1.08E-06	2.99E-06
SUPT3H	-1.52	5.13E-12	2.33E-11
SLC44A3	-1.52	1.17E-11	5.15E-11
UNC93B1	-1.52	6.48E-37	1.19E-35
SLC38A6	-1.52	1.32E-13	6.69E-13
NDUFA1	-1.51	4.88E-40	1.01E-38
TMEM205	-1.51	4.08E-37	7.58E-36
ZCRB1	-1.51	2.46E-88	2.13E-86
BRSK1	-1.50	7.65E-10	2.86E-09
HDACS	-1.50	3.47E-33	5.53E-32
RNASEH2B	-1.50	1.90E-22	1.76E-21
CLASRP	-1.50	4.14E-23	3.98E-22
CAMK1	-1.50	1.12E-21	1.00E-20
C11orf10	-1.49	1.26E-42	2.91E-41
PRKCSH	-1.49	5.06E-129	9.41E-127
PMF1-BGLAP	-1.49	3.71E-34	6.12E-33
NFASC	-1.49	1.16E-05	2.86E-05
LTBP4	-1.49	2.21E-61	9.29E-60
LAMA5	-1.49	2.31E-160	6.08E-158
LRSAM1	-1.49	5.65E-26	6.42E-25
CTSH	-1.48	6.14E-31	8.67E-30
HEXB	-1.48	7.22E-108	8.96E-106
MGST2	-1.48	1.97E-09	7.13E-09
FAH	-1.48	8.07E-22	7.23E-21
PEX7	-1.48	2.91E-14	1.56E-13
C5	-1.48	1.05E-11	4.64E-11
ACADS	-1.48	2.02E-21	1.76E-20
IFT43	-1.47	9.38E-15	5.24E-14
JAK3	-1.47	6.46E-12	2.90E-11
MRPL39	-1.47	1.89E-45	4.88E-44
SLC43A1	-1.47	3.84E-08	1.23E-07
EFEMP2	-1.47	9.20E-07	2.56E-06
SSBP4	-1.47	1.48E-14	8.14E-14
IMMP1L	-1.47	1.82E-07	5.46E-07

**Table 3 continued**

Gene symbol	logFC	P value	FDR
GPR108	-1.47	1.33E-60	5.50E-59
WDR54	-1.46	4.01E-38	7.75E-37
ARHGAP8	-1.46	4.37E-14	2.32E-13
RPL35A	-1.46	8.72E-183	2.76E-180
GBP2	-1.46	7.43E-12	3.31E-11
TECR	-1.46	1.15E-73	6.86E-72
AUH	-1.46	1.97E-08	6.54E-08
PRR5-ARHGAP8	-1.46	1.99E-14	1.08E-13
LINC00263	-1.45	7.89E-17	5.07E-16
PDLIM2	-1.45	2.48E-44	6.06E-43
RASA2	-1.45	1.41E-19	1.09E-18
PTPN6	-1.45	1.25E-36	2.27E-35
PARL	-1.45	2.07E-65	1.00E-63
CERCAM	-1.45	1.71E-74	1.04E-72
RPL37A	-1.45	3.14E-201	1.14E-198
ARRDC3	-1.45	2.82E-84	2.26E-82
NAE1	-1.45	1.38E-78	9.72E-77
MYZAP	-1.45	7.55E-09	2.60E-08
FBXO2	-1.44	3.57E-23	3.45E-22
C1QL1	-1.44	1.45E-18	1.05E-17
FDPS	-1.44	1.12E-208	4.30E-206
FER1L4	-1.44	2.19E-34	3.63E-33
TMEM8B	-1.44	2.90E-24	3.00E-23
THOC6	-1.44	1.49E-31	2.17E-30
DMPK	-1.43	9.94E-26	1.11E-24
RNF181	-1.43	1.88E-42	4.26E-41
GUK1	-1.43	3.52E-94	3.37E-92
GHDC	-1.43	2.52E-15	1.47E-14
GRAMD1A	-1.43	1.76E-70	9.52E-69
SYTL2	-1.43	3.67E-25	3.98E-24
LEPR	-1.43	7.79E-22	7.01E-21
FLJ22184	-1.43	9.59E-18	6.57E-17
EXOSC9	-1.42	5.87E-47	1.59E-45
MMAB	-1.42	2.11E-37	4.00E-36
KRT86	-1.42	1.20E-05	2.96E-05
ABHD1	-1.42	7.52E-08	2.34E-07
HOOK2	-1.42	1.59E-22	1.48E-21
PCSK4	-1.42	1.40E-10	5.56E-10
TMC6	-1.42	1.82E-28	2.31E-27
GDPD1	-1.42	6.19E-06	1.57E-05
LRRC23	-1.42	5.41E-11	2.25E-10
PION	-1.42	3.83E-12	1.75E-11
BCL7C	-1.42	9.48E-37	1.73E-35
YPEL3	-1.41	2.79E-10	1.08E-09
RAD51B	-1.41	7.17E-15	4.03E-14
ANXA4	-1.41	3.39E-64	1.55E-62
B4GALNT4	-1.41	8.74E-13	4.18E-12
COX7B	-1.41	1.11E-66	5.56E-65
PRKZ	-1.41	1.76E-15	1.03E-14
RAB4B	-1.41	2.43E-21	2.10E-20
C4orf34	-1.40	1.44E-38	2.81E-37
STXIO	-1.40	2.42E-15	1.41E-14
CRELD2	-1.40	5.50E-24	5.57E-23

**Table 3 continued**

Gene symbol	logFC	P value	FDR
ATP5E	-1.39	6.27E-93	5.87E-91
ESD	-1.39	1.48E-75	9.39E-74
MIA-RAB4B	-1.39	1.84E-21	1.61E-20
NDUFA13	-1.39	5.54E-58	2.17E-56
SNX14	-1.39	3.32E-75	2.09E-73
MRPL13	-1.39	2.86E-44	6.97E-43
PTPRH	-1.39	7.14E-18	4.93E-17
BBS5	-1.39	2.36E-32	3.55E-31
LMBRD1	-1.38	4.17E-25	4.50E-24
IQCH	-1.38	4.75E-08	1.51E-07
LMTK3	-1.38	4.13E-14	2.19E-13
MIR497HG	-1.38	6.24E-12	2.81E-11
C6orf70	-1.38	3.13E-25	3.41E-24
FGGY	-1.38	5.12E-07	1.46E-06
UNC5CL	-1.38	1.66E-08	5.52E-08
DUT	-1.38	8.03E-114	1.13E-111
P2RX4	-1.38	2.17E-20	1.76E-19
HHIPL2	-1.38	4.20E-06	1.09E-05
COX5A	-1.38	3.09E-79	2.21E-77
CKLF	-1.37	6.08E-34	9.94E-33
CRYZL1	-1.37	7.16E-27	8.45E-26
GSTM4	-1.37	6.05E-20	4.80E-19
DNAH14	-1.37	3.44E-11	1.45E-10
TCTN1	-1.37	6.80E-12	3.05E-11
CBX3P2	-1.36	2.01E-06	5.42E-06
PTH1R	-1.36	0.000133911	0.000291689
SEMA6C	-1.36	2.31E-09	8.29E-09
PIR	-1.36	2.10E-31	3.03E-30
DRAP1	-1.36	2.70E-101	2.90E-99
SCP2	-1.36	1.15E-12	5.47E-12
GMDS	-1.36	8.89E-18	6.10E-17
FRG1B	-1.36	9.55E-13	4.56E-12
DECR1	-1.35	4.15E-35	7.08E-34
CTAGE5	-1.35	4.25E-40	8.82E-39
NPM3	-1.35	1.82E-40	3.82E-39
AASS	-1.35	2.75E-05	6.49E-05
ZC3H6	-1.35	1.11E-29	1.48E-28
C6orf203	-1.35	2.06E-08	6.82E-08
ADAMTS13	-1.35	1.19E-11	5.23E-11
UBXN11	-1.35	2.01E-06	5.42E-06
C10orf54	-1.35	3.00E-63	1.32E-61
LSS	-1.35	7.02E-41	1.49E-39
KLC4	-1.35	7.74E-09	2.66E-08
ITGB3BP	-1.35	6.76E-11	2.78E-10
TKTL1	-1.35	2.72E-12	1.26E-11
C10orf55	-1.34	1.16E-63	5.16E-62
CRELD1	-1.34	1.99E-20	1.62E-19
ADSSL1	-1.34	2.20E-21	1.91E-20
ALKBH7	-1.34	1.62E-27	1.97E-26
AIFM3	-1.34	5.13E-07	1.47E-06
LLGL2	-1.34	2.44E-09	8.76E-09
SLC27A1	-1.34	1.99E-13	9.99E-13
ZBTB8OS	-1.34	5.50E-20	4.37E-19

**Table 3 continued**

Gene symbol	logFC	P value	FDR
ANKRD13D	-1.34	7.36E-25	7.86E-24
C6orf57	-1.34	3.31E-07	9.64E-07
GCAT	-1.33	8.16E-10	3.04E-09
TEX9	-1.33	1.32E-05	3.23E-05
MAP2K5	-1.33	9.00E-11	3.66E-10
SLC27A2	-1.33	2.27E-21	1.97E-20
LTBP3	-1.33	2.53E-43	5.95E-42
LOC100287559	-1.33	4.09E-05	9.47E-05
IFITM10	-1.33	9.64E-09	3.28E-08
CRYL1	-1.33	6.22E-10	2.34E-09
USH1C	-1.33	4.48E-09	1.57E-08
ZC3H12D	-1.33	0.000330901	0.000684453
ERI2	-1.32	7.33E-09	2.53E-08
TBX6	-1.32	0.000899671	0.001760238
WBSCR22	-1.32	1.53E-55	5.53E-54
GNB2L1	-1.32	2.65E-272	1.40E-269
LOC100131089	-1.32	3.24E-08	1.05E-07
EGFL7	-1.32	8.28E-37	1.52E-35
PIM3	-1.31	6.31E-67	3.18E-65
NUCB1	-1.31	1.86E-79	1.34E-77
FDXR	-1.31	1.08E-19	8.38E-19
EMID1	-1.31	2.72E-09	9.72E-09
PIBF1	-1.31	2.54E-16	1.58E-15
HIBCH	-1.30	1.13E-15	6.72E-15
RPS7	-1.30	4.23E-158	1.05E-155
BIK	-1.30	5.76E-06	1.47E-05
TCP11L2	-1.30	9.98E-07	2.77E-06
TSNAX-DISC1	-1.30	6.33E-22	5.72E-21
OMA1	-1.30	1.35E-25	1.50E-24
LOC100506990	-1.30	3.51E-09	1.24E-08
TSTD1	-1.30	7.46E-28	9.23E-27
KISS1R	-1.30	0.000386067	0.000792495
BCKDHA	-1.29	2.10E-43	4.98E-42
B9D1	-1.29	3.14E-13	1.56E-12
ZNF695	-1.29	8.45E-10	3.14E-09
TMEM63B	-1.29	2.19E-69	1.17E-67
MOSPD3	-1.29	8.70E-19	6.37E-18
RNASE4	-1.29	2.00E-27	2.42E-26
UGGT2	-1.29	6.04E-21	5.06E-20
SEMA3F	-1.29	2.32E-19	1.77E-18
RPS24	-1.29	6.92E-214	2.83E-211
DAK	-1.29	4.77E-62	2.04E-60
LOC100130691	-1.29	0.000198722	0.0004236
CTU2	-1.29	1.68E-13	8.48E-13
PLD3	-1.29	7.26E-45	1.81E-43
RHOV	-1.29	2.06E-15	1.20E-14
CHPT1	-1.29	5.19E-67	2.64E-65
ACSM3	-1.29	3.03E-11	1.29E-10
RPS25	-1.28	4.03E-185	1.31E-182
OASL	-1.28	2.48E-11	1.06E-10
RPLP1	-1.28	7.23E-219	3.05E-216
C19orf79	-1.28	2.43E-11	1.04E-10
IL20RB	-1.28	1.18E-09	4.32E-09

**Table 3 continued**

Gene symbol	logFC	P value	FDR
CACNG6	-1.28	1.23E-05	3.02E-05
TBCE	-1.28	1.40E-28	1.78E-27
FBXO16	-1.28	0.00019181	0.000409623
LOC100505549	-1.28	9.29E-06	2.31E-05
LOC100507218	-1.28	0.000213956	0.000453549
TLR5	-1.28	0.000112273	0.000247109
EML2	-1.28	1.54E-14	8.42E-14
NPM1	-1.28	3.12E-138	6.48E-136
GAA	-1.28	1.30E-32	1.99E-31
NKD2	-1.28	4.23E-10	1.61E-09
CRIP2	-1.28	8.19E-11	3.34E-10
LOC100132891	-1.27	6.71E-07	1.89E-06
ALG5	-1.27	2.16E-16	1.35E-15
PXK	-1.27	1.02E-14	5.67E-14
ADA	-1.27	6.11E-14	3.20E-13
GALE	-1.27	3.38E-45	8.55E-44
PHGDH	-1.27	3.96E-113	5.44E-111
CREG2	-1.27	0.000426556	0.000871508
MSLN	-1.27	2.53E-19	1.93E-18
GDPD5	-1.27	1.22E-12	5.80E-12
ITGA7	-1.27	5.07E-06	1.30E-05
LIG1	-1.27	1.36E-27	1.66E-26
LRTOMT	-1.26	4.37E-06	1.13E-05
C17orf49	-1.26	1.37E-44	3.39E-43
HMGNS	-1.26	5.93E-07	1.69E-06
LOC100505624	-1.26	4.04E-10	1.55E-09
CATSPER1	-1.25	0.000949224	0.00184719
TLE2	-1.25	2.35E-16	1.46E-15
CE53	-1.25	5.98E-07	1.70E-06
TTC35	-1.25	7.52E-30	1.01E-28
C6orf72	-1.25	2.65E-33	4.23E-32
RPS19	-1.25	1.01E-168	2.84E-166
EVI5L	-1.25	3.82E-23	3.68E-22
LOC81691	-1.25	7.76E-11	3.17E-10
PLEKHH3	-1.25	5.91E-39	1.17E-37
LOC100507501	-1.24	1.34E-06	3.67E-06
SLC25A5-AS1	-1.24	2.22E-20	1.80E-19
RPS8	-1.24	1.41E-201	5.25E-199
PPP1R7	-1.24	3.54E-37	6.58E-36
MAGED2	-1.24	4.04E-41	8.64E-40
CSTF3	-1.24	1.10E-12	5.24E-12
LINC00467	-1.24	1.39E-17	9.42E-17
MAD2L2	-1.24	4.26E-29	5.54E-28
PCCB	-1.24	2.05E-53	6.87E-52
SEZ6L2	-1.24	1.72E-27	2.09E-26
FKBP2	-1.24	8.99E-30	1.20E-28
DOCK6	-1.24	4.80E-35	8.13E-34
WIPI1	-1.24	2.07E-06	5.57E-06
ECH1	-1.23	5.12E-76	3.32E-74
OCEL1	-1.23	7.19E-14	3.74E-13
ZNF385C	-1.23	2.37E-06	6.31E-06
ATP8B3	-1.23	6.42E-24	6.47E-23
PAFAH1B2	-1.23	8.05E-25	8.57E-24

**Table 3 continued**

Gene symbol	logFC	P value	FDR
TM4SF19-TCTEX1D	-1.23	1.23E-05	3.02E-05
SRPX	-1.23	5.84E-11	2.42E-10
SLC39A11	-1.23	3.03E-21	2.60E-20
TMEM41B	-1.22	5.82E-09	2.02E-08
PADI2	-1.22	3.51E-11	1.48E-10
STX4	-1.22	8.39E-28	1.03E-26
MAP4K2	-1.22	1.86E-20	1.51E-19
PXMP4	-1.22	2.50E-07	7.39E-07
TCIRG1	-1.22	2.38E-41	5.15E-40
SERPING1	-1.22	8.23E-08	2.55E-07
IFI35	-1.22	4.92E-13	2.41E-12
DPY19L1P1	-1.22	3.99E-07	1.15E-06
MAN2B1	-1.22	5.94E-48	1.67E-46
FAF1	-1.22	5.28E-51	1.65E-49
ZDHHC1	-1.22	2.34E-06	6.25E-06
NAAA	-1.21	4.63E-11	1.93E-10
EFCAB11	-1.21	4.21E-05	9.73E-05
HSCB	-1.21	1.67E-12	7.85E-12
FBXW9	-1.21	2.21E-05	5.28E-05
ZNF467	-1.21	1.19E-09	4.36E-09
ILVBL	-1.21	1.32E-44	3.28E-43
SDR16C5	-1.21	4.72E-17	3.09E-16
IQGAP2	-1.21	6.21E-07	1.76E-06
SRGAP3	-1.21	2.76E-05	6.50E-05
EGF	-1.21	0.000108319	0.000238866
ERGIC3	-1.21	2.97E-63	1.31E-61
CYFIP2	-1.21	3.35E-14	1.79E-13
BCAS3	-1.21	5.34E-23	5.11E-22
DOCK11	-1.21	3.15E-11	1.33E-10
SLC37A1	-1.21	1.67E-07	5.02E-07
HSD17B4	-1.21	1.16E-54	4.10E-53
NT5M	-1.21	7.71E-05	0.000172918
SERINC5	-1.20	2.82E-06	7.46E-06
CCDC85B	-1.20	9.58E-95	9.54E-93
ALDH7A1	-1.20	1.18E-61	5.00E-60
OPLAH	-1.20	1.60E-21	1.41E-20
ASNS	-1.20	4.29E-106	5.17E-104
KIFAP3	-1.20	4.03E-26	4.60E-25
C1R	-1.20	2.83E-07	8.29E-07
FRY	-1.20	0.000920901	0.001797881
ANO9	-1.20	7.19E-07	2.02E-06
BCAM	-1.20	7.19E-33	1.11E-31
MED30	-1.20	1.06E-13	5.46E-13
LOC100127983	-1.20	6.85E-06	1.73E-05
CBS	-1.20	1.10E-55	4.00E-54
PNPLA2	-1.19	7.09E-37	1.30E-35
C1QL4	-1.19	1.08E-07	3.32E-07
LOC100129716	-1.19	0.000363791	0.000749078
ANKRD36BP2	-1.19	0.000287863	0.000599766
LCMT1	-1.19	7.16E-13	3.45E-12
SHF	-1.19	3.46E-06	9.04E-06
RABGGTA	-1.19	2.76E-10	1.07E-09
ANKRA2	-1.19	4.84E-15	2.76E-14

**Table 3 continued**

Gene symbol	logFC	P value	FDR
SYT12	-1.19	8.47E-20	6.64E-19
PYROXD2	-1.19	2.34E-06	6.25E-06
COPG2	-1.19	2.42E-35	4.16E-34
RAP1GAP	-1.19	1.26E-08	4.24E-08
LOC728743	-1.18	2.13E-05	5.11E-05
SRI	-1.18	5.42E-43	1.27E-41
DDX43	-1.18	2.82E-23	2.74E-22
PRIM1	-1.18	1.39E-29	1.85E-28
FAM125A	-1.18	2.67E-16	1.65E-15
HCFC1R1	-1.18	6.80E-52	2.20E-50
THBS3	-1.18	3.57E-18	2.51E-17
C15orf48	-1.18	6.58E-30	8.85E-29
C11orf54	-1.18	7.03E-18	4.86E-17
CTSF	-1.18	5.63E-26	6.40E-25
CDH3	-1.18	4.89E-59	1.96E-57
ULK4	-1.18	0.000777011	0.001532576
C15	-1.17	6.98E-05	0.00015741
VSIG1	-1.17	0.000372512	0.00076579
MED25	-1.17	6.05E-19	4.47E-18
AIG1	-1.17	7.65E-17	4.93E-16
VAV1	-1.17	2.41E-14	1.30E-13
PPA2	-1.17	1.32E-33	2.13E-32
FAM98C	-1.17	5.33E-05	0.000121815
FCGRT	-1.17	1.69E-26	1.95E-25
EXOSC8	-1.17	1.71E-25	1.88E-24
TMEM160	-1.17	1.88E-11	8.15E-11
SREBF1	-1.17	2.51E-32	3.78E-31
Clorf172	-1.17	8.99E-06	2.24E-05
MSI2	-1.17	1.73E-11	7.52E-11
IMPA2	-1.17	6.70E-36	1.17E-34
IGFBP6	-1.17	1.04E-18	7.55E-18
EIF2D	-1.17	7.55E-48	2.12E-46
LTA4H	-1.16	7.60E-76	4.88E-74
ASL	-1.16	7.72E-28	9.53E-27
ETHE1	-1.16	1.72E-23	1.69E-22
RPH3AL	-1.16	4.72E-21	3.99E-20
KLHDC2	-1.16	2.62E-74	1.59E-72
FAM171A2	-1.16	2.02E-09	7.29E-09
IFT88	-1.16	2.41E-07	7.15E-07
SIGIRR	-1.16	1.53E-05	3.72E-05
SUGT1	-1.16	1.60E-19	1.23E-18
TXNIP	-1.16	3.34E-07	9.72E-07
GTF2H2D	-1.16	0.000102722	0.000227077
REEP6	-1.15	1.93E-18	1.38E-17
AAAS	-1.15	5.67E-34	9.29E-33
CDKL2	-1.15	0.000611109	0.001221929
MRC2	-1.15	2.67E-32	4.02E-31
RPN2	-1.15	4.07E-177	1.26E-174
FN3K	-1.15	5.62E-11	2.36E-10
ST14	-1.15	5.82E-11	2.41E-10
GRAPL	-1.15	0.002321122	0.004253204
CUEDC2	-1.15	2.06E-28	2.59E-27
IFI30	-1.15	1.81E-08	6.01E-08

**Table 3 continued**

Gene symbol	logFC	P value	FDR
C9orf46	-1.15	1.24E-12	5.89E-12
ABCA5	-1.15	1.85E-07	5.53E-07
RPGR	-1.15	2.48E-07	7.34E-07
PKN1	-1.15	2.23E-84	1.80E-82
ATG16L2	-1.15	1.06E-06	2.95E-06
WBSCR27	-1.15	3.77E-06	9.80E-06
LRRC45	-1.14	1.24E-17	8.40E-17
PTMS	-1.14	1.81E-79	1.31E-77
CKLF-CMTM1	-1.14	1.06E-16	6.72E-16
BTC	-1.14	3.10E-05	7.27E-05
TNFSF12-TNFS*13	-1.14	7.55E-19	5.53E-18
PREX1	-1.14	4.53E-09	1.58E-08
FGD3	-1.14	7.45E-05	0.000167354
PCIF1	-1.14	2.14E-34	3.56E-33
CALB2	-1.14	3.17E-06	8.33E-06
PTGES	-1.14	3.74E-21	3.18E-20
HES7	-1.13	0.003803794	0.00674057
FGFR4	-1.13	8.06E-24	8.07E-23
NFKBID	-1.13	0.00094651	0.001842867
BMP1	-1.13	1.37E-31	2.00E-30
MSI1	-1.13	0.002464428	0.004500152
RPS6KB2	-1.13	2.74E-20	2.21E-19
KCTD19	-1.13	3.06E-06	8.06E-06
CCDC88B	-1.13	1.55E-11	6.73E-11
SCNN1A	-1.13	4.23E-35	7.21E-34
POMGNT1	-1.13	8.85E-41	1.88E-39
HECTD2	-1.13	0.001588305	0.002987874
NUP107	-1.13	2.10E-54	7.31E-53
CXCL16	-1.13	5.14E-12	2.33E-11
GAPDHS	-1.13	0.001914622	0.003556771
CDC42BPG	-1.13	3.79E-08	1.22E-07
MLXIPL	-1.12	6.00E-06	1.53E-05
IFI27L1	-1.12	1.31E-13	6.68E-13
ABCA7	-1.12	5.03E-32	7.44E-31
CREB3L4	-1.12	8.76E-17	5.61E-16
COPE	-1.12	1.68E-31	2.44E-30
PEMT	-1.12	4.08E-08	1.31E-07
PKN3	-1.12	2.05E-12	9.57E-12
UQCRC1	-1.12	3.06E-84	2.42E-82
DNAJC4	-1.12	2.58E-15	1.50E-14
FAM175A	-1.12	3.67E-05	8.54E-05
FIBP	-1.12	1.34E-48	3.86E-47
KCNN1	-1.12	1.14E-05	2.82E-05
RQCD1	-1.12	5.66E-19	4.19E-18
JUNB	-1.11	9.88E-50	2.95E-48
ASPSR1	-1.11	5.66E-13	2.76E-12
QPCTL	-1.11	4.68E-25	5.04E-24
CD9	-1.11	3.02E-94	2.91E-92
SH2B2	-1.11	6.68E-05	0.000151083
SSR4	-1.11	1.05E-19	8.16E-19
NDUFA2	-1.11	8.18E-19	5.99E-18
ALPK1	-1.11	1.89E-16	1.19E-15
GFM2	-1.11	1.22E-54	4.29E-53

**Table 3 continued**

Gene symbol	logFC	P value	FDR
GPCPD1	-1.11	8.79E-19	6.43E-18
NDRG2	-1.11	1.37E-06	3.74E-06
PRSS22	-1.11	0.002080435	0.003844256
MST1P9	-1.11	0.002266527	0.004161499
TRIM9	-1.11	0.000204924	0.000435644
ATP2A3	-1.11	4.09E-09	1.44E-08
TMEM161A	-1.11	2.06E-12	9.63E-12
ING4	-1.11	5.53E-08	1.75E-07
METTL5	-1.11	9.00E-34	1.46E-32
IFT74	-1.11	2.99E-11	1.27E-10
GALT	-1.10	9.23E-14	4.76E-13
ZCWPW2	-1.10	2.10E-32	3.17E-31
USH1G	-1.10	0.002619829	0.004769462
FAM162A	-1.10	1.90E-18	1.36E-17
BCL3	-1.10	3.72E-46	9.84E-45
TSPAN1	-1.10	9.28E-12	4.11E-11
SIPA1	-1.10	2.57E-25	2.80E-24
WDR27	-1.10	8.86E-07	2.47E-06
LOC678655	-1.10	2.98E-09	1.06E-08
MATN2	-1.10	3.00E-17	1.98E-16
SERPIN1	-1.10	7.67E-07	2.15E-06
NPRL2	-1.10	8.74E-12	3.88E-11
IRF6	-1.10	3.53E-11	1.49E-10
C17orf57	-1.10	9.25E-06	2.30E-05
HSPB11	-1.10	2.47E-11	1.06E-10
LOXL2	-1.10	2.56E-119	4.11E-117
GATS	-1.10	3.88E-07	1.12E-06
POLD1	-1.10	3.61E-38	6.98E-37
KREMEN2	-1.10	0.000906345	0.001771925
SH3YL1	-1.09	7.15E-18	4.93E-17
HEXDC	-1.09	3.33E-08	1.08E-07
CHIC2	-1.09	5.08E-05	0.000116308
FLJ39051	-1.09	0.000444045	0.000904903
ALKBH6	-1.09	4.88E-09	1.70E-08
MAGOH	-1.09	1.09E-14	6.06E-14
LOC100505783	-1.09	1.52E-05	3.70E-05
C16orf62	-1.09	1.35E-24	1.42E-23
GAL3ST1	-1.09	0.004091279	0.00721967
ZNF670-ZNF695	-1.09	6.71E-07	1.89E-06
UGCG	-1.09	2.19E-49	6.44E-48
AS3MT	-1.09	0.000326442	0.000675804
GRTP1	-1.09	2.37E-05	5.64E-05
AQP3	-1.09	3.02E-08	9.82E-08
TMEM45B	-1.09	7.62E-14	3.95E-13
ZP3	-1.09	2.43E-08	7.96E-08
AP4M1	-1.09	8.43E-09	2.89E-08
PLD1	-1.09	2.70E-06	7.14E-06
CCBL2	-1.09	2.76E-20	2.23E-19
NR4A1	-1.08	4.86E-21	4.10E-20
BRE	-1.08	1.97E-33	3.15E-32
PCYOX1L	-1.08	3.06E-15	1.77E-14
KIAA1456	-1.08	4.80E-05	0.000110264
AARS	-1.08	1.30E-192	4.43E-190

**Table 3 continued**

Gene symbol	logFC	P value	FDR
MRPL47	-1.08	2.55E-16	1.58E-15
ERP44	-1.08	4.10E-42	9.20E-41
ARHGEF16	-1.08	5.13E-13	2.51E-12
TP53TG1	-1.08	1.83E-05	4.40E-05
FA2H	-1.08	1.77E-08	5.89E-08
ADAM15	-1.07	4.71E-73	2.73E-71
STAG3	-1.07	0.005718352	0.00986248
PTK2B	-1.07	4.07E-14	2.16E-13
NSMCE1	-1.07	5.38E-18	3.74E-17
ATXN10	-1.07	9.31E-82	6.97E-80
CCDC53	-1.07	3.48E-15	2.01E-14
MIPEP	-1.07	4.92E-10	1.87E-09
TNFAIP2	-1.07	1.57E-146	3.48E-144
PSMA5	-1.07	1.18E-41	2.60E-40
INSIG1	-1.07	8.19E-55	2.90E-53
KIAA1383	-1.07	4.15E-06	1.07E-05
SDC2	-1.07	3.27E-05	7.64E-05
COX5B	-1.07	7.29E-32	1.08E-30
DTX4	-1.07	2.75E-06	7.28E-06
LOC100289495	-1.07	7.59E-05	0.000170296
BIN1	-1.07	8.92E-11	3.62E-10
CLDN7	-1.07	2.52E-17	1.68E-16
LMF1	-1.07	1.18E-05	2.90E-05
C11orf93	-1.07	0.000180253	0.000386051
C1RL	-1.06	2.49E-30	3.42E-29
MTMR11	-1.06	8.82E-20	6.91E-19
CST6	-1.06	4.12E-16	2.53E-15
CRISPLD1	-1.06	1.71E-07	5.16E-07
PFKL	-1.06	3.28E-73	1.92E-71
IER5L	-1.06	1.03E-19	8.04E-19
NUDT17	-1.06	2.65E-07	7.80E-07
RABAC1	-1.06	9.34E-31	1.31E-29
ABCA2	-1.06	2.56E-49	7.50E-48
TRAP1	-1.06	1.61E-76	1.05E-74
BBS9	-1.06	1.98E-11	8.56E-11
MMP15	-1.06	3.72E-27	4.45E-26
SCPEP1	-1.06	4.13E-22	3.76E-21
TLL2	-1.06	4.28E-05	9.90E-05
VPS28	-1.06	3.44E-19	2.60E-18
TCN2	-1.06	9.31E-07	2.59E-06
HS1BP3	-1.06	5.55E-20	4.41E-19
HMG20B	-1.06	9.18E-84	7.22E-82
FUCA1	-1.06	4.76E-18	3.32E-17
ARHGEF7	-1.05	1.63E-11	7.10E-11
WDR33	-1.05	6.18E-10	2.33E-09
SYT13	-1.05	0.004669962	0.008171303
C16orf13	-1.05	3.16E-24	3.26E-23
KTN1	-1.05	6.31E-91	5.75E-89
GPX4	-1.05	4.33E-82	3.26E-80
RPS16	-1.05	2.85E-107	3.46E-105
AGXT2L2	-1.05	1.67E-12	7.88E-12
TMEM141	-1.05	1.52E-18	1.09E-17
LAMP3	-1.05	4.66E-06	1.20E-05

**Table 3 continued**

Gene symbol	logFC	P value	FDR
CDKN1C	-1.05	0.000424019	0.000866884
LOC100288846	-1.05	0.000988006	0.001917938
DHRS12	-1.05	0.008237024	0.013823818
ATP6AP1L	-1.05	0.008191315	0.013754406
ERCC2	-1.05	4.13E-23	3.98E-22
FMOS	-1.05	0.008652057	0.014449416
ULK2	-1.05	8.06E-20	6.33E-19
SMARCD3	-1.05	2.06E-08	6.82E-08
PHYHD1	-1.05	4.25E-11	1.78E-10
C10orf11	-1.05	0.003354135	0.006000913
KRTCAP3	-1.05	0.000203547	0.000433154
SRP54	-1.05	2.70E-88	2.32E-86
IMMP2L	-1.04	2.06E-07	6.13E-07
CARS	-1.04	3.50E-44	8.52E-43
RPL24	-1.04	5.98E-76	3.86E-74
GSN	-1.04	3.51E-17	2.31E-16
BAI2	-1.04	9.31E-16	5.58E-15
WDR18	-1.04	1.17E-46	3.16E-45
ZC4H2	-1.04	0.009400904	0.015597066
EIF3M	-1.04	4.78E-59	1.93E-57
SLC25A42	-1.04	7.39E-08	2.30E-07
MTHFR	-1.04	2.62E-10	1.02E-09
ABCG2	-1.04	0.003349706	0.005994684
NR1H3	-1.04	0.000505923	0.001023253
PAAF1	-1.04	2.18E-21	1.90E-20
GSTK1	-1.04	1.65E-37	3.13E-36
DEPDC4	-1.04	0.000125031	0.000273146
ZNF396	-1.04	2.31E-05	5.51E-05
BHLHE40	-1.04	2.30E-66	1.15E-64
TECPR1	-1.04	3.48E-13	1.72E-12
AMN1	-1.04	1.59E-07	4.80E-07
NTPCR	-1.04	3.26E-21	2.79E-20
MVD	-1.04	5.49E-40	1.13E-38
RRAS	-1.04	1.37E-24	1.44E-23
LOC144481	-1.03	0.001555384	0.00293074
SURF1	-1.03	1.48E-25	1.64E-24
MFF	-1.03	1.03E-98	1.09E-96
MAGED1	-1.03	3.74E-72	2.11E-70
TBL3	-1.03	7.98E-25	8.51E-24
DYX1C1	-1.03	0.000142357	0.000309076
SLC16A5	-1.03	2.35E-23	2.30E-22
GPRIN2	-1.03	1.03E-10	4.17E-10
LOC100130015	-1.03	2.39E-07	7.07E-07
DDX60	-1.03	0.000267213	0.000559136
MITD1	-1.03	1.44E-11	6.27E-11
RBP1	-1.03	0.006467371	0.011039757
TBCA	-1.03	5.18E-33	8.15E-32
ICAM5	-1.03	5.23E-14	2.75E-13
TNFRSF10C	-1.03	0.00023491	0.000494816
CPE	-1.03	7.1E-14	3.70E-13
ANK2	-1.03	3.67E-11	1.54E-10
C22orf26	-1.03	0.000452354	0.000920647
SNX2	-1.03	6.73E-33	1.04E-31

**Table 3 continued**

Gene symbol	logFC	P value	FDR
ANXA3	-1.03	1.06E-78	7.48E-77
C15orf58	-1.02	0.00133034	0.002534258
RBX1	-1.02	1.31E-21	1.16E-20
ABCD1	-1.02	4.71E-08	1.50E-07
P4HA3	-1.02	0.000276213	0.00057711
KRBA2	-1.02	0.004111753	0.007253308
GLS2	-1.02	0.000259768	0.000544639
ENDOG	-1.02	5.93E-08	1.87E-07
COX7C	-1.02	6.09E-67	3.08E-65
C8orf59	-1.02	2.88E-20	2.32E-19
RAB11FIP4	-1.02	6.08E-09	2.11E-08
CDKL1	-1.02	8.11E-06	2.03E-05
LOC100133957	-1.02	0.001919501	0.003564787
DENND1A	-1.02	5.20E-33	8.18E-32
TRAM1	-1.02	1.47E-76	9.69E-75
UPK3B	-1.02	9.22E-07	2.56E-06
ANKRD29	-1.02	1.13E-27	1.38E-26
CHMP5	-1.02	7.09E-56	2.61E-54
CCDC125	-1.02	4.05E-07	1.17E-06
MEF2BNB-MEF2B	-1.01	0.000476068	0.000966579
PTPRE	-1.01	2.62E-47	7.25E-46
MAGIX	-1.01	0.012672093	0.020531485
MDP1	-1.01	0.000316356	0.000656213
SEMA4G	-1.01	2.18E-21	1.90E-20
TRMT11	-1.01	7.49E-10	2.80E-09
TNFRSF9	-1.01	0.001333696	0.002540269
AMZ2P1	-1.01	1.77E-07	5.32E-07
C7orf10	-1.01	0.000709162	0.001406426
PRPF40B	-1.01	5.32E-24	5.39E-23
NCOA7	-1.01	8.97E-40	1.84E-38
MPND	-1.01	0.000182363	0.000390505
C17orf28	-1.01	1.33E-07	4.04E-07
PFDN5	-1.01	1.94E-57	7.44E-56
VWA1	-1.01	1.13E-18	8.22E-18
VPS33B	-1.01	4.79E-11	2.00E-10
PHYHIP	-1.00	2.49E-07	7.35E-07
SUSD2	-1.00	2.55E-29	3.35E-28
CCNA1	-1.00	1.64E-08	5.47E-08
GAMT	-1.00	4.53E-10	1.72E-09
SLC44A2	-1.00	2.72E-41	5.85E-40
ODF2L	-1.00	2.38E-16	1.48E-15
HIST1H1C	-1.00	2.07E-43	4.93E-42
TAF10	-1.00	6.64E-28	8.23E-27
AKT3	-1.00	7.55E-14	3.92E-13
MACROD2	-1.00	0.008868792	0.014782098
ADAM23	-1.00	1.90E-08	6.31E-08
COQ6	-1.00	2.59E-13	1.29E-12
DLEU2	-1.00	0.005572257	0.009628891
CAT	-1.00	1.55E-30	2.14E-29
MSMO1	-1.00	4.14E-33	6.57E-32
LOC100506334	-1.00	3.11E-06	8.17E-06
TARS2	-1.00	2.70E-38	5.25E-37
P4HTM	-1.00	1.17E-15	6.93E-15

**Table 3 continued**

Gene symbol	logFC	P value	FDR
EBF4	-1.00	0.001175315	0.002258326
ARHGEF26-AS1	-1.00	0.000118469	0.000259887
OSGEP1	-1.00	1.23E-11	5.41E-11
PPFIA3	-1.00	2.52E-05	5.96E-05
C19orf71	-1.00	1.03E-05	2.56E-05
CECR2	-1.00	0.000117675	0.000258236
NAT14	-0.99	1.20E-13	6.15E-13
FADS2	-0.99	2.47E-79	1.77E-77
CALCOCO1	-0.99	3.84E-18	2.69E-17
APOL1	-0.99	0.000590629	0.001183409
ITFG3	-0.99	2.53E-39	5.08E-38
KDELC1	-0.99	1.11E-06	3.05E-06
RPL3	-0.99	1.72E-158	4.35E-156
PLCL2	0.99	1.02E-08	3.47E-08
AOC2	0.99	5.20E-07	1.48E-06
ZBTB2	0.99	3.55E-64	1.61E-62
LOC387647	0.99	2.94E-28	3.68E-27
GDF11	0.99	1.84E-42	4.17E-41
LOC100130992	0.99	6.14E-14	3.21E-13
ZNF407	0.99	1.38E-21	1.22E-20
LOC100288615	0.99	2.15E-11	9.26E-11
TEX15	0.99	1.21E-49	3.59E-48
PMS2P5	0.99	2.22E-10	8.68E-10
TSPYL4	1.00	3.02E-31	4.33E-30
FICD	1.00	4.01E-07	1.16E-06
ZNF587	1.00	3.63E-30	4.94E-29
ANKRD50	1.00	4.80E-50	1.46E-48
NR5A2	1.00	3.61E-06	9.42E-06
ZBTB40	1.00	9.91E-30	1.32E-28
SLAMF7	1.00	1.57E-11	6.83E-11
LOC100129046	1.00	2.73E-07	8.03E-07
PHLPP2	1.00	2.77E-38	5.37E-37
ZNF267	1.00	7.57E-20	5.95E-19
FLNC	1.00	9.43E-158	2.29E-155
ZNF850	1.00	1.62E-14	8.85E-14
HOXB6	1.00	7.96E-27	9.37E-26
RNF34	1.00	6.70E-44	1.61E-42
FOXO3	1.01	5.30E-30	7.17E-29
HUS1	1.01	1.05E-20	8.65E-20
ZNF185	1.01	1.74E-82	1.33E-80
GJA1	1.01	6.19E-16	3.75E-15
AP1S2	1.01	1.54E-19	1.19E-18
TUBB2A	1.01	9.33E-18	6.40E-17
IL16	1.01	0.000167472	0.000360202
ZNF799	1.02	1.30E-09	4.76E-09
LOC100505648	1.02	0.000565896	0.001136915
FAM160A1	1.02	0.004606923	0.008071049
KCTD7	1.02	8.21E-16	4.95E-15
ZNF271	1.02	7.41E-78	5.06E-76
LOC401588	1.02	7.86E-08	2.44E-07
EIF5A	1.02	1.72E-190	5.72E-188
ABHD16B	1.02	1.13E-13	5.79E-13
NBPF15	1.03	4.54E-51	1.43E-49

**Table 3 continued**

Gene symbol	logFC	P value	FDR
LOC283922	1.03	0.001810781	0.003376264
GDAP1	1.03	2.93E-52	9.56E-51
KANSL1	1.03	2.80E-09	9.97E-09
HOXB5	1.03	4.62E-16	2.83E-15
LRRC37A4P	1.03	4.01E-19	3.00E-18
RCBTB2	1.04	0.003040041	0.005483952
MYB	1.04	7.95E-05	0.000177891
SLC35F3	1.04	4.08E-27	4.87E-26
LOC100287314	1.04	0.00752343	0.012712245
ZNF33A	1.04	7.90E-65	3.71E-63
TARDBP	1.04	2.43E-135	4.87E-133
FLJ42627	1.04	3.98E-10	1.52E-09
ZNF239	1.04	4.56E-32	6.76E-31
FAM86DP	1.04	1.66E-10	6.54E-10
IL1RL1	1.04	1.54E-08	5.17E-08
ZNF655	1.05	2.40E-34	3.98E-33
ZNF114	1.05	3.01E-18	2.13E-17
FAM35A	1.05	9.15E-46	2.38E-44
SIX2	1.05	0.000341596	0.000705559
ETS1	1.05	3.20E-96	3.24E-94
ERVK13-1	1.05	7.87E-08	2.45E-07
LOC100288123	1.05	0.003598851	0.006403414
SPATA13	1.05	5.28E-19	3.92E-18
PTGER2	1.06	9.55E-10	3.53E-09
METTL12	1.06	1.30E-08	4.37E-08
GNB3	1.06	0.000318505	0.000659914
NOG	1.06	0.001463904	0.002772409
LOC100379224	1.06	1.78E-12	8.34E-12
ZNF514	1.06	2.92E-18	2.07E-17
LOC100506649	1.06	1.27E-46	3.41E-45
CHORDC1	1.07	1.72E-57	6.60E-56
CDKN1A	1.07	7.51E-66	3.68E-64
ARMCX4	1.07	1.38E-14	7.62E-14
NBPF1	1.07	1.78E-24	1.86E-23
TJP2	1.07	8.04E-145	1.75E-142
LOC147804	1.07	1.07E-13	5.51E-13
PRDM13	1.07	2.87E-07	8.40E-07
SON	1.07	2.20E-170	6.31E-168
EPHB2	1.07	6.87E-09	2.37E-08
POM121C	1.08	7.93E-52	2.55E-50
ZNF443	1.08	2.53E-07	7.47E-07
JRK	1.08	7.15E-24	7.18E-23
KBTBD8	1.08	0.000226507	0.000478711
ASB16	1.08	1.81E-06	4.90E-06
FAM86B1	1.08	4.25E-08	1.36E-07
CREB5	1.08	8.91E-16	5.35E-15
VAMP1	1.08	4.97E-14	2.62E-13
USP32P1	1.08	3.37E-24	3.47E-23
IRGQ	1.08	4.72E-37	8.74E-36
RPS26	1.09	8.51E-106	1.02E-103
CLCN4	1.09	2.07E-11	8.92E-11
DPY19L2	1.09	1.60E-06	4.36E-06
TMPPE	1.10	0.000159821	0.000344921



**Table 3 continued**

Gene symbol	logFC	P value	FDR
RP9P	1.10	1.53E-14	8.36E-14
ZNF600	1.10	2.10E-16	1.32E-15
C17orf51	1.10	5.46E-47	1.48E-45
ABL2	1.10	6.59E-118	1.02E-115
ZRSR2	1.11	1.52E-05	3.70E-05
ATAD3B	1.11	3.55E-17	2.34E-16
ZBTB26	1.11	5.88E-14	3.08E-13
LOC100527964	1.11	0.000167054	0.00035964
RASSF10	1.11	0.001652544	0.003100419
WDR52	1.12	0.001376432	0.002616151
ENTPD7	1.12	2.86E-59	1.16E-57
KLHL21	1.12	1.76E-47	4.90E-46
SERPINB7	1.13	5.41E-06	1.39E-05
TFCP2L1	1.13	4.61E-16	2.82E-15
RFTN1	1.13	4.04E-18	2.83E-17
PTHLH	1.13	1.75E-07	5.26E-07
C10orf216	1.13	3.58E-29	4.66E-28
MGC57346	1.13	1.40E-09	5.11E-09
MALAT1	1.14	3.24E-113	4.51E-111
NSUN5P1	1.14	1.10E-06	3.03E-06
C3orf52	1.14	8.59E-13	4.12E-12
MRPS25	1.14	4.61E-67	2.35E-65
C11orf41	1.14	1.89E-08	6.29E-08
EPHA4	1.14	1.27E-05	3.12E-05
LOC283624	1.14	1.05E-22	9.88E-22
FRMD6	1.15	1.79E-118	2.83E-116
XRCC2	1.15	5.36E-36	9.41E-35
ATF5	1.15	7.98E-35	1.34E-33
NOV	1.15	0.000586861	0.00117642
RPL23AP64	1.15	0.000182902	0.00039146
FGF5	1.15	7.83E-05	0.00017528
DNAH17	1.16	5.10E-06	1.31E-05
PPARGC1B	1.16	8.77E-12	3.89E-11
PEA15	1.16	1.76E-127	3.19E-125
MIR22HG	1.16	1.55E-27	1.89E-26
LOC219731	1.16	5.88E-05	0.000133586
SLC7A2	1.16	4.67E-05	0.000107518
ZEB1	1.16	2.44E-37	4.58E-36
MOB3C	1.17	1.91E-22	1.77E-21
SBDSP1	1.17	6.56E-27	7.74E-26
LCAT	1.17	3.08E-08	9.99E-08
HBEGF	1.17	2.63E-45	6.70E-44
MGC70870	1.17	1.69E-109	2.14E-107
CDC42EP2	1.18	6.61E-33	1.03E-31
LOC440300	1.18	1.60E-20	1.31E-19
TMED10P1	1.19	1.35E-14	7.42E-14
B3GALT5	1.19	0.000161499	0.000348482
BMPER	1.19	4.12E-14	2.19E-13
HERC2P7	1.19	1.08E-15	6.44E-15
SEMA3A	1.20	3.81E-10	1.46E-09
HNRNPU-AS1	1.20	1.86E-28	2.35E-27
C20orf118	1.20	1.01E-08	3.43E-08
LOC154761	1.21	1.58E-05	3.84E-05

**Table 3 continued**

Gene symbol	logFC	P value	FDR
BTBD6	1.21	3.31E-124	5.74E-122
ALG10	1.21	3.97E-15	2.28E-14
LINC00338	1.22	2.07E-17	1.38E-16
RPL23AP7	1.22	5.87E-08	1.85E-07
CLDN15	1.22	3.94E-17	2.60E-16
TUBA4A	1.22	3.74E-64	1.69E-62
ZNF860	1.22	8.13E-19	5.96E-18
NBPFI0	1.23	1.33E-13	6.78E-13
EFNB2	1.23	5.00E-20	3.98E-19
C15orf52	1.24	3.83E-77	2.56E-75
RRS1	1.24	1.88E-119	3.05E-117
OXTR	1.24	1.09E-16	6.95E-16
CRMP1	1.25	1.15E-06	3.18E-06
ZNF440	1.25	3.58E-18	2.52E-17
EIF4EBP3	1.26	0.000648201	0.001292417
DUSP7	1.26	1.51E-29	1.99E-28
EXOG	1.26	8.37E-22	7.50E-21
MAMLD1	1.27	1.94E-25	2.14E-24
SMPD3	1.27	6.68E-09	2.31E-08
PNN	1.28	1.20E-105	1.42E-103
PMEPA1	1.28	1.35E-87	1.14E-85
SCARF1	1.29	2.58E-10	1.00E-09
LOC100505815	1.29	1.06E-07	3.24E-07
FBXL19-AS1	1.29	1.55E-13	7.86E-13
HIST1H4H	1.29	1.12E-08	3.80E-08
TUBB	1.30	1.63E-74	9.98E-73
LOC100289230	1.30	0.000190102	0.000406114
FAM111B	1.30	2.83E-117	4.27E-115
ZNF33B	1.30	1.31E-57	5.07E-56
ZNF121	1.30	1.57E-28	1.99E-27
ZNF780A	1.30	1.31E-25	1.45E-24
NEFM	1.30	2.06E-10	8.07E-10
DGCR11	1.30	1.08E-13	5.52E-13
ST20	1.31	5.79E-08	1.83E-07
ADAM1	1.32	7.15E-10	2.68E-09
SRSF1	1.32	1.55E-170	4.54E-168
LOC642846	1.33	2.29E-09	8.22E-09
LOC730755	1.33	4.02E-07	1.16E-06
ZNF594	1.33	2.96E-18	2.10E-17
ITGA2	1.33	7.36E-102	8.02E-100
RRN3P3	1.33	4.14E-10	1.58E-09
MXD1	1.34	2.31E-28	2.90E-27
PKI55	1.35	3.94E-10	1.51E-09
LOC100507433	1.35	9.28E-07	2.58E-06
PPAPDC1A	1.35	5.00E-27	5.95E-26
PIGW	1.35	7.76E-78	5.28E-76
NBPF9	1.35	3.18E-46	8.45E-45
ZNF782	1.36	4.73E-11	1.97E-10
RRP7B	1.36	4.18E-08	1.33E-07
MICA	1.36	1.68E-22	1.56E-21
SCARNA12	1.36	4.69E-05	0.000108075
DDX12P	1.36	1.67E-09	6.07E-09
RPSAP9	1.36	5.75E-08	1.81E-07

**Table 3 continued**

Gene symbol	logFC	P value	FDR
PLEKHM1	1.37	2.14E-08	7.05E-08
CLDN1	1.37	1.78E-123	2.99E-121
TUBB1	1.37	1.35E-07	4.10E-07
SERHL	1.37	2.41E-09	8.64E-09
YY2	1.38	1.99E-15	1.16E-14
LOC344595	1.38	8.64E-13	4.14E-12
LOC654342	1.39	1.44E-08	4.83E-08
HCN2	1.39	1.10E-05	2.71E-05
TSSK2	1.39	5.96E-06	1.52E-05
SERTAD4	1.40	4.02E-18	2.81E-17
PTGDR2	1.40	1.65E-14	8.98E-14
HTR7P1	1.40	5.99E-16	3.63E-15
C10rf63	1.41	2.97E-32	4.44E-31
OBF2A	1.41	1.26E-72	7.20E-71
ICOSLG	1.41	3.58E-23	3.46E-22
PPP1R3E	1.42	8.05E-22	7.22E-21
F13A1	1.42	1.56E-21	1.37E-20
WASH1	1.43	1.32E-13	6.69E-13
GNRH1	1.43	7.51E-09	2.59E-08
TLR2	1.44	2.19E-07	6.50E-07
PXDN	1.45	2.57E-18	1.83E-17
LOX	1.45	4.42E-65	2.11E-63
EIF3C	1.46	6.70E-21	5.60E-20
EIF3CL	1.46	6.74E-21	5.62E-20
DHRS4L2	1.46	4.24E-11	1.78E-10
CD274	1.46	6.02E-65	2.85E-63
LOC646329	1.46	4.89E-07	1.40E-06
ZNF767	1.46	6.55E-20	5.19E-19
SPNS2	1.46	4.72E-21	3.99E-20
LOC401431	1.47	1.10E-13	5.62E-13
SHISA7	1.47	1.52E-07	4.60E-07
WASH3P	1.47	1.01E-15	6.05E-15
C12orf34	1.47	6.88E-13	3.32E-12
LOC728643	1.47	6.16E-10	2.32E-09
PI4KAP1	1.48	3.11E-15	1.80E-14
HSPA8	1.48	0	0
BCL2A1	1.48	1.71E-11	7.41E-11
ADAMTS6	1.49	3.58E-06	9.33E-06
SPIN2B	1.49	1.12E-09	4.12E-09
TUBA1B	1.49	4.03E-278	2.32E-275
TNFAIP3	1.50	3.05E-159	7.86E-157
CCDC39	1.50	3.75E-05	8.72E-05
WASH5P	1.51	3.91E-50	1.19E-48
SPHK1	1.52	4.08E-27	4.87E-26
ZNF417	1.53	1.87E-17	1.25E-16
LOC100289019	1.53	3.60E-10	1.38E-09
TUBA1C	1.54	0	0
BMS1P5	1.54	2.70E-06	7.16E-06
BMS1P1	1.54	2.71E-06	7.17E-06
SHISA9	1.54	1.40E-48	4.04E-47
SOX9	1.54	1.14E-50	3.52E-49
ENC1	1.55	3.65E-104	4.24E-102
PLEKHA8P1	1.55	4.63E-10	1.76E-09

**Table 3 continued**

Gene symbol	logFC	P value	FDR
NEAT1	1.55	2.74E-226	1.24E-223
LOC100506123	1.55	6.41E-12	2.88E-11
LOC100506599	1.56	1.30E-08	4.37E-08
FOXO3B	1.56	4.19E-17	2.76E-16
PDIA3P	1.56	1.88E-19	1.44E-18
MMP1	1.56	6.14E-19	4.53E-18
FERMT1	1.57	9.62E-144	2.06E-141
NPTX2	1.57	2.39E-07	7.07E-07
MSTO2P	1.58	3.96E-15	2.27E-14
ZFP112	1.58	2.53E-18	1.80E-17
AFG3L1P	1.59	3.41E-74	2.05E-72
TFRC	1.60	1.56E-210	6.16E-208
SPRN	1.63	3.15E-21	2.70E-20
LOC100133091	1.64	4.17E-08	1.33E-07
GKN2	1.64	1.01E-19	7.88E-19
LOC100272217	1.64	8.20E-08	2.54E-07
LOC100132247	1.66	1.26E-11	5.53E-11
UBC	1.67	0	0
LOC440894	1.69	4.98E-07	1.42E-06
HERC2P2	1.70	1.86E-84	1.51E-82
CBWD2	1.70	2.67E-09	9.56E-09
DQX1	1.71	1.13E-10	4.53E-10
CHRM3	1.72	1.40E-14	7.68E-14
TMEM158	1.72	1.85E-29	2.44E-28
G0S2	1.73	4.26E-70	2.29E-68
LOC100288778	1.77	5.61E-13	2.74E-12
CCZ1	1.81	6.97E-29	9.02E-28
GPR89A	1.81	6.11E-21	5.12E-20
DOK3	1.83	1.00E-10	4.05E-10
C6orf141	1.85	7.97E-58	3.11E-56
NAV3	1.85	1.21E-68	6.33E-67
HERC2P9	1.85	9.07E-20	7.09E-19
GOLGA8B	1.86	5.17E-113	7.03E-111
OPHN1	1.93	1.05E-64	4.92E-63
TAGLN	1.94	2.23E-95	2.24E-93
PRG4	1.95	6.72E-29	8.72E-28
NBPF16	1.95	1.02E-114	1.48E-112
AGAP6	1.96	2.09E-25	2.30E-24
PFN1P2	2.05	1.19E-30	1.65E-29
PPP1R11	2.18	2.28E-16	1.42E-15
HMGA2	2.19	7.78E-56	2.85E-54
SRSF10	2.22	1.64E-22	1.53E-21
GOLGA8A	2.30	1.62E-88	1.41E-86
LOC100216001	2.32	1.88E-13	9.49E-13
NBPF14	2.34	4.08E-85	3.35E-83
LOC284454	2.42	2.30E-69	1.22E-67
ESM1	2.55	6.08E-25	6.53E-24
LOC613037	2.70	2.83E-23	2.74E-22

library were determined by the University of Missouri DNA core. Deep sequencing was performed by the MU DNA core using Illumina HiSeq 2000 following the

**Table 4 Gene ontology analysis of Esrrb-dependent DY131-altered genes**

Term (down-regulated genes)	Count	P value
GO:0042273 ~ ribosomal large subunit biogenesis	4	0.007
GO:0006297 ~ nucleotide-excision repair, DNA gap filling	4	0.032
GO:0006541 ~ glutamine metabolic process	4	0.042
GO:0009083 ~ branched chain family amino acid catabolic process	5	0.001
GO:0042274 ~ ribosomal small subunit biogenesis	5	0.001
GO:0009081 ~ branched chain family amino acid metabolic process	5	0.004
GO:0006904 ~ vesicle docking during exocytosis	5	0.016
GO:0048278 ~ vesicle docking	5	0.021
GO:0006958 ~ complement activation, classical pathway	5	0.031
GO:0022406 ~ membrane docking	5	0.038
GO:0002455 ~ humoral immune response mediated by circulating immunoglobulin	6	0.008
GO:0009060 ~ aerobic respiration	6	0.014
GO:0006635 ~ fatty acid beta-oxidation	7	0.001
GO:0009062 ~ fatty acid catabolic process	7	0.003
GO:0019395 ~ fatty acid oxidation	7	0.005
GO:0034440 ~ lipid oxidation	7	0.005
GO:0033559 ~ unsaturated fatty acid metabolic process	7	0.019
GO:0009064 ~ glutamine family amino acid metabolic process	7	0.020
GO:0019228 ~ regulation of action potential in neuron	7	0.024
GO:0006289 ~ nucleotide-excision repair	7	0.026
GO:0051591 ~ response to cAMP to cAMP	8	0.002
GO:0006800 ~ oxygen and reactive oxygen species metabolic process	8	0.021
GO:0001508 ~ regulation of action potential	8	0.023
GO:0009566 ~ fertilization	8	0.046
GO:0044242 ~ cellular lipid catabolic process	9	0.013
GO:0007160 ~ cell-matrix adhesion	9	0.032
GO:0060627 ~ regulation of vesicle-mediated transport	9	0.046
GO:0009063 ~ cellular amino acid catabolic process	10	0.002
GO:0045333 ~ cellular respiration	10	0.020
GO:0007568 ~ aging	10	0.040
GO:0016485 ~ protein processing	10	0.044
GO:0006364 ~ rRNA processing	11	0.005
GO:0016072 ~ rRNA metabolic process	11	0.007
GO:0006887 ~ exocytosis	11	0.022
GO:0009310 ~ amine catabolic process	12	0.000
GO:0008203 ~ cholesterol metabolic process	12	0.001
GO:0016125 ~ sterol metabolic process	12	0.003
GO:0042391 ~ regulation of membrane potential	12	0.024
GO:0015980 ~ energy derivation by oxidation of organic compounds	12	0.038
GO:0042254 ~ ribosome biogenesis	13	0.005
GO:0016053 ~ organic acid biosynthetic process	14	0.013
GO:0046394 ~ carboxylic acid biosynthetic process	14	0.013
GO:0022613 ~ ribonucleoprotein complex biogenesis	14	0.038
GO:0016042 ~ lipid catabolic process	15	0.013
GO:0006457 ~ protein folding	15	0.016
GO:0034470 ~ ncRNA processing	15	0.025
GO:0022900 ~ electron transport chain	16	0.000
GO:0032940 ~ secretion by cell	16	0.026
GO:0016054 ~ organic acid catabolic process	17	0.000

**Table 4 continued**

Term (down-regulated genes)	Count	P value
GO:0046395 ~ carboxylic acid catabolic process	17	0.000
GO:0034660 ~ ncRNA metabolic process	19	0.008
GO:0006631 ~ fatty acid metabolic process	21	0.000
GO:0046903 ~ secretion	22	0.014
GO:0006414 ~ translational elongation	25	0.000
GO:0008610 ~ lipid biosynthetic process	26	0.002
GO:0006091 ~ generation of precursor metabolites and energy	31	0.000
GO:0006412 ~ translation	38	0.000
GO:0016192 ~ vesicle-mediated transport	39	0.003
GO:0055114 ~ oxidation reduction	54	0.000
Term (up-regulated genes)	Count	P value
GO:0002220 ~ innate immune response activating cell surface receptor signaling pathway	2	0.045
GO:0048712 ~ negative regulation of astrocyte differentiation	2	0.045
GO:0000724 ~ double-strand break repair via homologous recombination	3	0.020
GO:0000725 ~ recombinational repair	3	0.020
GO:0045987 ~ positive regulation of smooth muscle contraction	4	0.001
GO:0045933 ~ positive regulation of muscle contraction	4	0.002
GO:0006940 ~ regulation of smooth muscle contraction	4	0.009
GO:0050768 ~ negative regulation of neurogenesis	4	0.015
GO:0010721 ~ negative regulation of cell development	4	0.018
GO:0006937 ~ regulation of muscle contraction	4	0.050
GO:0048704 ~ embryonic skeletal system morphogenesis	5	0.004
GO:0048706 ~ embryonic skeletal system development	5	0.012
GO:0031344 ~ regulation of cell projection organization	5	0.019
GO:0007411 ~ axon guidance	5	0.035
GO:0051258 ~ protein polymerization	6	0.000
GO:0043623 ~ cellular protein complex assembly	6	0.039
GO:0050767 ~ regulation of neurogenesis	6	0.042
GO:0048705 ~ skeletal system morphogenesis	7	0.002
GO:0060284 ~ regulation of cell development	7	0.031
GO:0007018 ~ microtubule-based movement	8	0.000
GO:0051960 ~ regulation of nervous system development	8	0.007
GO:0006916 ~ anti-apoptosis	8	0.010
GO:0007017 ~ microtubule-based process	8	0.027
GO:0001501 ~ skeletal system development	9	0.031
GO:0006917 ~ induction of apoptosis	9	0.031
GO:0012502 ~ induction of programmed cell death	9	0.032
GO:0045596 ~ negative regulation of cell differentiation	10	0.001
GO:0040008 ~ regulation of growth	10	0.017
GO:0043066 ~ negative regulation of apoptosis	10	0.021
GO:0043069 ~ negative regulation of programmed cell death	10	0.023
GO:0060548 ~ negative regulation of cell death	10	0.023
GO:0022403 ~ cell cycle phase	10	0.049
GO:0006928 ~ cell motion	12	0.021
GO:0042127 ~ regulation of cell proliferation	17	0.018
GO:0042981 ~ regulation of apoptosis	18	0.011
GO:0043067 ~ regulation of programmed cell death	18	0.012
GO:0010941 ~ regulation of cell death	18	0.012
GO:0006355 ~ regulation of transcription, DNA-dependent	29	0.047

**Table 4 continued**

Term (up-regulated genes)	Count	P value
GO:0051252 ~ regulation of RNA metabolic process	30	0.038
GO:0006350 ~ transcription	43	0.000
GO:0045449 ~ regulation of transcription	48	0.001

manufacturer's instruction. Briefly, samples (8 total) were pooled into one lane with each sample annealed to a specific indexed adaptor. 50 bp single end reads were generated. For each sample, approximately 18 million reads were generated in fastq format (NCBI-GEO, accession number: GSE71208). The sequencing reads were trimmed and filtered using FASTX-Toolkit (V 0.0.13) ([http://hannonlab.cshl.edu/fastx\\_toolkit](http://hannonlab.cshl.edu/fastx_toolkit)), and mapped to genome (UCSC hg18) using TopHat2 [39, 40]. Gene expression values were determined by gene raw read counts using an in-house tool MULTICOM-MAP [41–43]. Raw reads were normalized to each sample's library size and differentially expressed genes were calculated using R/Bioconductor package edgeR [44]. Specifically, we kept the genes that have at least 1 count-per-million (cpm) in at least 2 samples and computed the effective library sizes. Pairwise gene expression tests were carried out using exact test. Differentially expressed genes were determined by log<sub>2</sub> fold change (Log<sub>2</sub>FC) (Log<sub>2</sub>FC ≥ 1, or Log<sub>2</sub>FC ≤ -1), p value (p < 0.05) and false discovery rate (FDR < 0.05) [45].

#### Gene set function enrichment

Gene ontology (GO) analysis was performed using DAVID bioinformatics sources 6.7 [46, 47]. Differentially expressed genes from certain pairwise comparisons were uploaded to DAVID server (<http://david.abcc.ncifcrf.gov>) and GO analysis were performed for biological process (BP). Minimum counts were set as default value (two counts) and maximum EASE score (p value) was set to 0.05. Differentially expressed genes pathway enrichment analysis was performed using Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway [48, 49]. Gene expression profiles Spearman ranking correlation analysis was analyzed using R (version 3.0.2). Gene expression heat map and hierarchical clustering were created by R/Bioconductor (version 2.13) package gplot.

#### Statistical analysis

qPCR experiments were performed in triplicate on both biological replicates. T test was employed to statistically analyze whether the differences in gene expression is significant (p < 0.05). Statistical significance of gene set overlap (Venn Diagram) are tested according to previous reported method [17].

#### Availability of supporting data

The data sets supporting the results of this article are available in the NCBI-GEO repository, accession number: GSE71208, URL: <http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE71208>.

#### Additional files

**Additional file 1: Figure S1.** DY131-activated Esrrb regulates p21. **Figure S2.** Full gel images.

**Additional file 2: Table S1.** Gene ontology analysis result. **Table S2.** Esrrb expression with DY131 treatment (control vs. Esrrb + DY131).

#### Abbreviations

Esrrb: estrogen related receptor beta; ERRE: estrogen related receptor response element; SFRE: steroid factor response element; iPSC: induced pluripotent stem cells; OSKM: Oct4, Sox2, Klf4, cMyc; FBS: fetal bovine serum; RT: reverse transcriptase; KEGG: Kyoto encyclopedia of genes and genomes; GO: gene ontology; FC: fold change; Esrrg: estrogen related receptor gamma.

#### Authors' contributions

YL established the model cell line and performed RNA isolation, Esrrb expression status test, western blot, cell growth assay, differentially expressed gene analysis, functional enrichment of gene sets by GO and KEGG pathway, construct gene regulation network and statistical analysis. YL, JL, JC performed sequence alignment and generated the gene expression count table for RNA-seq data analysis. YL and DBL conceived of the study, participated in its design and drafted the manuscript. All authors read and approved the final manuscript.

#### Author details

<sup>1</sup> Department of Biochemistry, University of Missouri, Columbia, MO 65211, USA. <sup>2</sup> MU Center for Botanical Interaction Studies, University of Missouri, Columbia, MO 65211, USA. <sup>3</sup> Computer Science Department, University of Missouri, Columbia, MO 65211, USA. <sup>4</sup> Informatics Institute, University of Missouri, Columbia, MO 65211, USA. <sup>5</sup> Xiphophorus Genetic Stock Center, Texas State University, San Marcos, TX 78666, USA.

#### Acknowledgements

We thank Dr. Wei Zhou for cloning Esrrb. We also thank Nicholas Starkey, Benjamin Merideth and Yufei Li for helpful discussions. This publication or project was made possible in part by Grant Number P50AT006273 from the National Center for Complementary and Integrative Health (NCCIH), the Office of Dietary Supplements (ODS), and the National Cancer Institute (NCI). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCCAM, ODS, NCI, or the National Institutes of Health.

#### Competing interests

The authors declare that they have no competing interests.

Received: 28 June 2015 Accepted: 13 November 2015

Published online: 01 December 2015

## References

- Giguere V, Yang N, Segui P, Evans RM. Identification of a new class of steroid hormone receptors. *Nature*. 1988;331:91–4.
- Vanacker JM, Pettersson K, Gustafsson JA, Laudet V. Transcriptional targets shared by estrogen receptor-related receptors (ERRs) and estrogen receptor (ER) alpha, but not by ERbeta. *EMBO J*. 1999;18:4270–9.
- Luo J, Sladek R, Bader JA, Matthyssens A, Rossant J, et al. Placental abnormalities in mouse embryos lacking the orphan nuclear receptor ERR-beta. *Nature*. 1997;388:778–82.
- Zhou W, Liu Z, Wu J, Liu JH, Hyder SM, et al. Identification and characterization of two novel splicing isoforms of human estrogen-related receptor beta. *J Clin Endocrinol Metab*. 2006;91:569–79.
- Welstead GG, Brambrink T, Jaenisch R. Generating iPSC cells from MEFS through forced expression of Sox-2, Oct-4, c-Myc, and Klf4. *J Vis Exp*. 2008;14.
- Feng B, Jiang J, Kraus P, Ng JH, Heng JC, et al. Reprogramming of fibroblasts into induced pluripotent stem cells with orphan nuclear receptor Esrrb. *Nat Cell Biol*. 2009;11:197–203.
- Buganim Y, Faddah DA, Cheng AW, Itskovich E, Markoulaki S, et al. Single-cell expression analyses during cellular reprogramming reveal an early stochastic and a late hierarchic phase. *Cell*. 2012;150:1209–22.
- Cheung CP, Yu S, Wong KB, Chan LW, Lai FM, et al. Expression and functional study of estrogen receptor-related receptors in human prostatic cells and tissues. *J Clin Endocrinol Metab*. 2005;90:1830–44.
- Yu S, Wong YC, Wang XH, Ling MT, Ng CF, et al. Orphan nuclear receptor estrogen-related receptor-beta suppresses in vitro and in vivo growth of prostate cancer cells via p21(WAF1/CIP1) induction and as a potential therapeutic target in prostate cancer. *Oncogene*. 2008;27:3313–28.
- Fujimura T, Takahashi S, Urano T, Ijichi N, Ikeda K, et al. Differential expression of estrogen-related receptors beta and gamma (ERRbeta and ERRgamma) and their clinical significance in human prostate cancer. *Cancer Sci*. 2010;101:646–51.
- Zhou W, Lo SC, Liu JH, Hannink M, Lubahn DB. ERRbeta: a potent inhibitor of Nrf2 transcriptional activity. *Mol Cell Endocrinol*. 2007;278:52–62.
- Bombail V, Collins F, Brown P, Saunders PT. Modulation of ER alpha transcriptional activity by the orphan nuclear receptor ERR beta and evidence for differential effects of long- and short-form splice variants. *Mol Cell Endocrinol*. 2010;314:53–61.
- Chen X, Xu H, Yuan P, Fang F, Huss M, et al. Integration of external signaling pathways with the core transcriptional network in embryonic stem cells. *Cell*. 2008;133:1106–17.
- Ouyang Z, Zhou Q, Wong WH. ChIP-Seq of transcription factors predicts absolute and differential gene expression in embryonic stem cells. *Proc Natl Acad Sci USA*. 2009;106:21521–6.
- Percharde M, Laval F, Ng JH, Kumar V, Tomaz RA, et al. Nco3 functions as an essential Esrrb coactivator to sustain embryonic stem cell self-renewal and reprogramming. *Genes Dev*. 2012;26:2286–98.
- Nishiyama A, Sharov AA, Piao Y, Amano M, Amano T, et al. Systematic repression of transcription factors reveals limited patterns of gene expression changes in ES cells. *Sci Rep*. 2013;3:1390.
- Zhou Q, Chipperfield H, Melton DA, Wong WH. A gene regulatory network in mouse embryonic stem cells. *Proc Natl Acad Sci USA*. 2007;104:16438–43.
- Carter MG, Stagg CA, Falco G, Yoshikawa T, Bassey UC, et al. An in situ hybridization-based screen for heterogeneously expressed genes in mouse ES cells. *Gene Expr Patterns*. 2008;8:181–98.
- van den Berg DL, Zhang W, Yates A, Engelen E, Takacs K, et al. Estrogen-related receptor beta interacts with Oct4 to positively regulate Nanog gene expression. *Mol Cell Biol*. 2008;28:5986–95.
- Zhang X, Zhang J, Wang T, Esteban MA, Pei D. Esrrb activates Oct4 transcription and sustains self-renewal and pluripotency in embryonic stem cells. *J Biol Chem*. 2008;283:35825–33.
- Storm MP, Kumpfmüller B, Thompson B, Kolde R, Vilo J, et al. Characterization of the phosphoinositide 3-kinase-dependent transcriptome in murine embryonic stem cells: identification of novel regulators of pluripotency. *Stem Cells*. 2009;27:764–75.
- Gao M, Sun P, Wang J, Zhao D, Wei L. Expression of estrogen receptor-related receptor isoforms and clinical significance in endometrial adenocarcinoma. *Int J Gynecol Cancer*. 2006;16:827–33.
- Wang SC, Myers S, Dooms C, Capon R, Muscat GE. An ERRbeta/gamma agonist modulates GRalpha expression, and glucocorticoid responsive gene expression in skeletal muscle cells. *Mol Cell Endocrinol*. 2010;315:146–52.
- Byerly MS, Al Salayta M, Swanson RD, Kwon K, Peterson JM, et al. Estrogen-related receptor beta deletion modulates whole-body energy balance via estrogen-related receptor gamma and attenuates neuropeptide Y gene expression. *Eur J Neurosci*. 2013;37:1033–47.
- Byerly MS, Swanson RD, Wong GW, Blackshaw S. Estrogen-related receptor beta deficiency alters body composition and response to restraint stress. *BMC Physiol*. 2013;13:10.
- Castet A, Herledan A, Bonnet S, Jalaguier S, Vanacker JM, et al. Receptor-interacting protein 140 differentially regulates estrogen receptor-related receptor transactivation depending on target genes. *Mol Endocrinol*. 2006;20:1035–47.
- Sumi D, Ignarro LJ. Estrogen-related receptor alpha 1 up-regulates endothelial nitric oxide synthase expression. *Proc Natl Acad Sci USA*. 2003;100:14451–6.
- Vanacker JM, Bonnelye E, Chopin-Delannoy S, Delmarre C, Cavailles V, et al. Transcriptional activities of the orphan nuclear receptor ERR alpha (estrogen receptor-related receptor-alpha). *Mol Endocrinol*. 1999;13:764–73.
- Abe S, Usami S, Nakamura Y. Mutations in the gene encoding KIAA1199 protein, an inner-ear protein expressed in Deiters' cells and the fibrocytes, as the cause of nonsyndromic hearing loss. *J Hum Genet*. 2003;48:564–70.
- He QY, Liu XH, Li Q, Studholme DJ, Li XW, et al. G8: a novel domain associated with polycystic kidney disease and non-syndromic hearing loss. *Bioinformatics*. 2006;22:2189–91.
- Guo J, Cheng H, Zhao S, Yu L. GG: a domain involved in phage LTF apparatus and implicated in human MEB and non-syndromic hearing loss diseases. *FEBS Lett*. 2006;580:581–4.
- Michishita E, Garces G, Barrett JC, Horikawa I. Upregulation of the KIAA1199 gene is associated with cellular mortality. *Cancer Lett*. 2006;239:71–7.
- Collin RW, Kalay E, Tariq M, Peters T, van der Zwaag B, et al. Mutations of ESRRB encoding estrogen-related receptor beta cause autosomal-recessive nonsyndromic hearing impairment DFNB35. *Am J Hum Genet*. 2008;82:125–38.
- Ben Said M, Ayedi L, Mnejja M, Hakim B, Khalfallah A, et al. A novel missense mutation in the ESRRB gene causes DFNB35 hearing loss in a Tunisian family. *Eur J Med Genet*. 2011;54:e535–41.
- Lee K, Khan S, Ansar M, Santos-Cortez RL, Ahmad W, et al. A novel ESRRB deletion is a rare cause of autosomal recessive nonsyndromic hearing impairment among Pakistani families. *Genet Res Int*. 2011;2011:368915.
- Safka Brozkova D, Lastuvkova J, Machalova E, Lisonova J, Trkova M, et al. DFNB35 due to a novel mutation in the ESRRB gene in a Czech consanguineous family. *Int J Pediatr Otorhinolaryngol*. 2012;76:1681–4.
- Lee EK, Han GY, Park HW, Song YJ, Kim CW. Transgelin promotes migration and invasion of cancer stem cells. *J Proteom Res*. 2010;9:5108–17.
- Welshons WV, Grady LH, Engler KS, Judy BM. Control of proliferation of MCF-7 breast cancer cells in a commercial preparation of charcoal-stripped adult bovine serum. *Breast Cancer Res Treat*. 1992;23:97–104.
- Langmead B, Trapnell C, Pop M, Salzberg SL. Ultrafast and memory-efficient alignment of short DNA sequences to the human genome. *Genome Biol*. 2009;10:R25.
- Trapnell C, Pachter L, Salzberg SL. TopHat: discovering splice junctions with RNA-Seq. *Bioinformatics*. 2009;25:1105–11.
- Sun L, Fernandez HR, Donohue RC, Li J, Cheng J, et al. Male-specific lethal complex in Drosophila counteracts histone acetylation and does not mediate dosage compensation. *Proc Natl Acad Sci USA*. 2013;110:E808–17.
- Sun L, Johnson AF, Donohue RC, Li J, Cheng J, et al. Dosage compensation and inverse effects in triple X metafemales of Drosophila. *Proc Natl Acad Sci USA*. 2013;110:7383–8.
- Sun L, Johnson AF, Li J, Lambdin AS, Cheng J, et al. Differential effect of aneuploidy on the X chromosome and genes with sex-biased expression in Drosophila. *Proc Natl Acad Sci USA*. 2013;110:16514–9.
- Robinson MD, McCarthy DJ, Smyth GK. edgeR: a Bioconductor package for differential expression analysis of digital gene expression data. *Bioinformatics*. 2010;26:139–40.
- Li H, Lovci MT, Kwon YS, Rosenfeld MG, Fu XD, et al. Determination of tag density required for digital transcriptome analysis: application to an androgen-sensitive prostate cancer model. *Proc Natl Acad Sci USA*. 2008;105:20179–84.

46. da Huang W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat Protoc.* 2009;4:44–57.
47. da Huang W, Sherman BT, Lempicki RA. Bioinformatics enrichment tools: paths toward the comprehensive functional analysis of large gene lists. *Nucleic Acids Res.* 2009;37:1–13.
48. Kanehisa M, Goto S, Sato Y, Kawashima M, Furumichi M, et al. Data, information, knowledge and principle: back to metabolism in KEGG. *Nucleic Acids Res.* 2014;42:D199–205.
49. Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res.* 2000;28:27–30.

Submit your next manuscript to BioMed Central  
and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at  
[www.biomedcentral.com/submit](http://www.biomedcentral.com/submit)

