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## Olanzapine Reversed Brain Gene Expression Changes Induced by Phencyclidine Treatment in Non-Human Primates

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#### **Key Words**

Schizophrenia · Antipsychotics · Gene expression · Phencyclidine · Cynomolgus monkey · Prefrontal cortex

## Abstract

The NMDA receptor antagonist phencyclidine (PCP) creates schizophrenia-like symptoms in normal controls. The effect of PCP on non-human primate brain gene expression was examined and compared to changes induced by olanzapine treatment. Experimental studies of PCP and antipsychotic drugs have direct relevance to understanding the pathophysiology and treatment of schizophrenia. Genome-wide changes in prefrontal cortex gene expression revealed alterations of 146 transcripts in the PCP treatment group compared to vehicle controls. Dysregulated genes were enriched in identified classes implicated in neurological and genetic disorders, including schizophrenia genes from the Psychiatric Genomics Consortium 108 loci as well as cell death in PCP-treated primates. Canonical pathway analysis revealed a significant overrepresentation of several groups including synaptic long-term potentiation and calcium signaling. Olanzapine coadministered with PCP normalized 34% of the 146 PCP-induced probe set expression changes, and a network of 17 olanzapine-normalized genes was identified enriched in schizophrenia candidate genes containing RGS4,

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E-Mail karger@karger.com www.karger.com/mnp SYN1 and AKT as nodes. The results of this study support the use of PCP administration in non-human primates as a glutamatergic model of schizophrenia and suggest that a large number of PCP-induced expression differences can be reversed by olanzapine. The results of this study may be informative for identification of potential candidates for pharmacogenetics and biomarker research related to the treatment of schizophrenia. © 2015 S. Karger AG, Basel

## Introduction

Schizophrenia is a highly heritable disorder characterized by positive, negative, and cognitive symptoms. Current antipsychotic treatments for schizophrenia are modifications of serendipitous discoveries and primarily involve antagonism of dopamine and serotonin receptors. The molecular mechanism of action of antipsychotics remains to be elucidated. To date, genome-wide changes in gene expression in response to antipsychotic treatment have not been assessed in a non-human primate model of schizophrenia. The purpose of this study was to examine the effects of antipsychotic administration on whole-genome prefrontal cortex (PFC) gene expression in a primate model of schizophrenia.

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Group	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Acute
VEH	VEH	VEH	VEH	VEH	VEH	VEH	VEH
РСР	PCP (1 mg/kg/day)	PCP (1 mg/kg/day)	PCP (2 mg/kg/day)	PCP (2 mg/kg/day)	PCP (2 mg/kg/day)	PCP (2 mg/kg/day)	VEH
PCP + OLZ	PCP (1 mg/kg/day)	PCP (1 mg/kg/day)	PCP (2 mg/kg/day)/ OLZ (0.75 mg/kg b.i.d.)	VEH			
OLZ	VEH	VEH	OLZ (0.75 mg/kg b.i.d.)	VEH			
HAL	VEH	VEH	HAL (1.5 mg/kg b.i.d.)	VEH			
AOLZ	VEH	VEH	VEH	VEH	VEH	VEH	OLZ (3 mg/kg)
AHAL	VEH	VEH	VEH	VEH	VEH	VEH	HAL (8 mg/kg)

Table 1. Study design: cynomolgus monkeys were administered 1 of 6 drug regimens for up to 6 weeks

One commonly used pharmacological model of schizophrenia involves mimicking glutamate receptor hypofunction, which is hypothesized to play a role in the etiology of schizophrenia [1]. This model is partly based on the knowledge that NMDA receptor antagonists such as phencyclidine (PCP) exacerbate schizophrenia and produce positive and negative symptoms and cognitive deficits in schizophrenia [2, 3] as well as symptoms in subjects with no previous psychiatric history [4]. Although there is no complete animal model of schizophrenia, PCP blockade of NMDA receptors has been used in animals to model NMDA receptor hypofunction, which is hypothesized to be causally related to some clinical features of schizophrenia [5]. Other evidence of glutamate dysfunction in schizophrenia includes alterations in glutamate receptor subunits (for a review, see [6]). Moreover, clinical data have shown that an mGlu2/3 agonist is effective in reducing positive and negative symptoms in subjects with schizophrenia [7], while preclinical data have demonstrated that mGlu2/3 agonism decreases presynaptic glutamate activity and is effective in preventing the prefrontal increase in glutamate efflux due to PCP as well as PCP-induced behaviors in rats [8].

In the current study, cynomolgus monkeys were administered the NMDA receptor antagonist PCP with or without OLZ cotreatment to determine if genome-wide level changes could be reversed by antipsychotic administration.

#### **Materials and Methods**

#### Animals and Drug Treatments

Cynomolgus monkeys (n = 42) were randomly assigned to 1 of 6 drug groups and administered vehicle (VEH; saline and 10% acacia), the antipsychotics chronic haloperidol (HAL; 1.5 mg/kg), acute haloperidol (AHAL; 8.0 mg/kg), chronic olanzapine (OLZ;

0.75 mg/kg), or acute olanzapine (AOLZ; 3.0 mg/kg), the NMDA receptor antagonist PCP (1.0–2.0 mg/kg/day), or PCP and OLZ (PCP + OLZ). The duration of the drug administration over a 6-week period is described in table 1. The protocol was reviewed and approved by the Institutional Animal Care and Use Committee at Covance Laboratories Inc. (Madison, Wis., USA).

#### Dose Administration

The PCP hydrochloride or saline was administered via an ALZET Osmotic Pump (Model 2ML2, Lot No. 9910925; Alza Corporation, Palo Alto, Calif., USA). The 10% acacia or OLZ were administered orally after injecting the required volume into dried Calimyrna figs (Mariani Packing Co. Inc., Vacaville, Calif., USA). The method and dose of PCP administration used in the current study was the same as described previously [9], which was shown to produce serum PCP levels in primates similar to the range associated with psychosis-like behavioral consequences of PCP intoxication in humans. Each animal had three surgeries to implant an osmotic pump. Each pump was maintained for at least a 2-week infusion interval, then discarded and replaced with a new pump or discarded after removal at necropsy. Animals were anesthetized by administration of propofol A, and the osmotic pump was implanted subcutaneously in the scapular region. The sterile saline or PCP was administered by continuous subcutaneous infusion 7 days/ week for at least 6 weeks via an indwelling osmotic pump. Starting with the pm dose on day 1, 10% acacia was offered in figs to all animals twice daily (approx. 12 h apart). Beginning with the am dose on day 15 and continuing until the day 43 am dose, 10% acacia or OLZ preparations were offered in figs twice daily (approx. 12 h apart). The prepared suspensions were injected into 1 dried fig/animal for each dose. Animals were offered figs twice daily for at least 6 weeks.

#### Plasma Concentration Results

Mean plasma concentrations of PCP administered via the osmotic pumps were relatively proportional to the dose level. At the nominal dose level of 1 mg/kg/day, the mean PCP plasma concentration was 14.07  $\pm$  1.25 ng/ml for animals in the PCP group and 11.4  $\pm$  1.44 ng/ml for animals in the PCP + OLZ group on day 15. After doubling the nominal dose level to 2 mg/kg/day, the mean PCP plasma concentration was 23.05  $\pm$  2.01 ng/ml for animals in the PCP group and 19.20  $\pm$  1.60 ng/ml for animals in the PCP + OLZ group on day 36. Mean plasma concentrations of OLZ were

	Overall treatment	OLZ vs. VEH	PCP vs. VEH	PCP vs. PCP + OLZ
HG6800				
Nominal p value	1,952/1,897	198/190 (11↓, 187↑)	2,504/2,425 (2,502↓, 2↑)	1,796/1,735 (1,792↓, 4↑)
Bonferroni	54/53	3/3 (0↓, 3↑)	19/19 (19↓, 0↑)	18/18 (18↓, 0↑)
Step-up	801/785	5/5 (01, 51)	1,216/1,191 (1,215↓, 1↑)	295/288 (2951, 01)
HG-U95				
Nominal p value	400/361	48/45 (19↓, 29↑)	228/216 (215↓,13↑)	166/156 (129↓, 371)
Bonferroni	2/2	$0(0\downarrow,0\uparrow)$	$0(0\downarrow,0\uparrow)$	$1(1\downarrow,0\uparrow)$
Step-up	13/13	0(01,01)	0(01,01)	$1(1\downarrow,0\uparrow)$
Overlap				
Nominal p value	244	12 (0↓, 12↑)	146 (145↓,1↑)	85 (84↓, 1↑)
Bonferroni	2	0(01,01)	$0(0\downarrow,0\uparrow)$	$1(1\downarrow,0\uparrow)$
Step-up	8	0 (01, 01)	0 (01, 01)	1 (11, 01)

**Table 2.** Number of significant findings (p < 0.05) by microarray platform according to nominal p value, Bonferroni corrected p value, and FDR step-up corrected p value

The number of probesets/gene symbols is shown for each array. The overlap between both platforms is shown for the same comparisons in the last rows.

**Table 3.** IPA was used to functionally annotate 146 genes altered on both microarray platforms in the PCP treatment group compared to the VEH control group

Category	B-H p value	Genes, n
Neurological disease	4.59E-10	76
Genetic disorder	6.95E-10	92
Skeletal and muscular disorders	6.95E-10	64
Cell death	1.03E-09	69
Cancer	5.31E-07	32

IPA identified a significant over-representation of genes implicated in neurological disorders and genetic disorders, including schizophrenia (19 genes in total;  $p = 9 \times 10^{-5}$ ), after correcting for multiple comparisons with Benjamini-Hochberg (B-H) associated with PCP effects.

relatively consistent over the course of the study and within the range of plasma concentrations seen in humans after the administration of efficacious doses of OLZ [10]. The dose for OLZ was chosen to produce plasma concentrations that are within the range of drug concentrations observed after the administration of efficacious doses of OLZ in patients [10]. The mean OLZ plasma concentrations ranged between  $3.64 \pm 0.71$  and  $7.39 \pm 1.85$  ng/ml in the OLZ group and between  $6.92 \pm 1.74$  and  $16.20 \pm 4.31$  ng/ml in the PCP + OLZ group. This is within the range of concentrations observed in schizophrenia patients treated with 1–10 mg ( $1.47 \pm 0.77$  to  $20.68 \pm 17.07 \mu$ g/l). The mean HAL plasma concentrations were also relatively consistent over the course of the study and ranged between  $0.31 \pm 0.02$  and  $0.74 \pm 0.11$  ng/ml. The mean AHAL and AOLZ plasma concentrations were  $3.71 \pm 0.31$  and  $68.51 \pm 9.71$  ng/ml, respectively.

## Tissue Collection

After 6 weeks of treatment, animals were fasted overnight, then anesthetized with sodium pentobarbital, weighed, exsanguinated, and necropsied. From the right half of the brain, the anterior portion of the frontal cortex including Brodmann areas 9, 10, 11, 32 and 46 was carefully dissected, flash frozen in liquid nitrogen, and then stored in a freezer, set to maintain 60–80°C, until analyzed.

#### Microarray Detection of Probe Set Levels

Subjects were run in duplicate on two arrays (Affymetrix HU6800 and HG-U95A/HG-U95Av2) for a total of four arrays per animal. Double-stranded cDNA was synthesized from 10 µg of total RNA from each RNA extraction using the SuperScript Choice system (Gibco-BRL) with an oligo(dt) primer containing T7 RNA polymerase promoter (Geneset). The cDNA was purified by phenol/chloroform extraction. Biotin-labeled cRNA was synthesized and purified and hybridized to Affymetrix U95 or HU6800 microarrays. Microarrays were stained and washed on Affymetrix fluidics station 400 according to the manufacturer's instructions.

## Data Analysis

Data were analyzed with Partek Genomics Suite statistical software version 6.5 (St. Louis, Mo., USA). Two outliers were removed from both arrays based on visualization of principal components analysis scatter plot. A batch effect related to the scan date was observed by principal components analysis, and the scan date was used in ANCOVA to reduce this effect. The resulting data for each microarray platform were analyzed separately by a three-way ANOVA with array technical replicate, subject and treatment as factors, with subject nested within treatment. Results were corrected for multiple comparisons by Bonferroni correction or false discovery rate step-up correction.

## Functional Annotation Analyses

Genes with nominal p values <0.05 on both the U95 and HU6800 arrays and consistent fold change directions between arrays were

**Table 4.** IPA was queried with 146 genes altered on both microarray platforms in the PCP treatment group compared to the VEH controlgroup

Ingenuity canonical pathways	B-H p value	Genes
Huntington's disease signaling	$4.27\times10^{-7}$	MAPK1, PIK3R1, UBE2S, SNAP25, CDK5R1, PRKCG, DNM1, BCL2L1, MTOR, PRKCI,PENK, STX16, NCOR2, NAPA, RASA1
Melatonin signaling	$1.78  imes 10^{-5}$	PRKACB, CAMK4, PRKCI, MAPK1, RORB, PRKCG, PRKAR1A, CAMK2G
Neuropathic pain signaling in dorsal horn neurons	$1.78 \times 10^{-5}$	PRKACB, CAMK4, PRKCI, MAPK1, GRIA1, PIK3R1, PRKCG, PRKAR1A, CAMK2G
Synaptic long-term potentiation	$2.63 \times 10^{-5}$	PRKACB, CAMK4, PRKCI, MAPK1, GRIA1, PPP3CA, PRKCG, PRKAR1A, CAMK2G
Calcium signaling	$2.63 \times 10^{-5}$	PRKACB, CALR, CAMK4, MAPK1, GRIA1, MEF2C, ATP2A2, PPP3CA, ATP2B2, PRKAR1A, CAMK2G
Melatonin signaling Neuropathic pain signaling in dorsal horn neurons Synaptic long-term potentiation Calcium signaling	$   \begin{array}{r}     1.78 \times 10^{-5} \\     1.78 \times 10^{-5} \\     2.63 \times 10^{-5} \\     2.63 \times 10^{-5} \\   \end{array} $	PRKACB, CAMK4, PRKCI, MAPK1, RORB, PRKCG, PRKAR1A, CAMK PRKACB, CAMK4, PRKCI, MAPK1, GRIA1, PIK3R1, PRKCG, PRKAR1, CAMK2G PRKACB, CAMK4, PRKCI, MAPK1, GRIA1, PPP3CA, PRKCG, PRKAR1 CAMK2G PRKACB, CALR, CAMK4, MAPK1, GRIA1, MEF2C, ATP2A2, PPP3CA, ATP2B2, PRKAR1A, CAMK2G

IPA canonical pathway analysis identified the following over-represented canonical pathways after correcting for multiple comparisons. B-H = Benjamini-Hochberg.

used as input variables for the dataset to query the Ingenuity Pathways Analysis (IPA) software v7.1 canonical pathway analysis unless otherwise stated [11]. Gene symbols were mapped to the corresponding gene objects in the Ingenuity Pathways Knowledge Base. Each network or pathway was set to have a maximum of 35 focus genes. IPA identified those pathways containing direct and indirect relationships that were most significant to the input dataset. The significance of the association between the dataset and the canonical pathway was determined based on the Benjamini-Hochberg stepdown false discovery rate calculated with Fisher's exact test by calculating the probability that the association between the genes in the dataset and the canonical pathway is due to chance alone. Overrepresented related transcription factors were identified using DAVID Bioinformatics Database (http://david.abcc.ncifcrf.gov/).

## Results

## Antipsychotic Effects on Gene Expression

To assess treatment effects on gene expression, we identified genes with significant treatment effects on both the Affymetrix HU6800 and Affymetrix HG-U95A/HG-U95Av2 arrays. Genes with expression significantly associated with treatment at the p < 0.05 level with consistent fold change directions on both arrays were considered true treatment effect genes. A total of 7,130 probe sets were represented on the HU6800 array and 12,600 on the U95 array. A total of 5,282 unique gene symbols overlapped between arrays. The number of significant findings on each array and the overlap between arrays are outlined in table 2. All probe set data for the overlapping 5,282 genes on the U95 and HU6800 arrays are shown in

OLZ Reversed Brain Gene Expression Changes Induced by PCP online supplementary tables 1 and 2, respectively (see www.karger.com/doi/10.1159/000430786 for all online suppl. material).

## PCP Effects on PFC Gene Expression

There were a total of 146 overlapping genes with nominally significantly altered gene expression at p < 0.05 in PCP-administered animals compared to VEH controls on the U95 and HU6800 arrays. All but one gene were downregulated in PCP-administered animals compared to VEH controls. Genes that were significant at the p < p0.05 level on both arrays with consistent fold change directions are listed in online supplementary table 3. IPA was used to functionally annotate the 146 genes and identified a significant overrepresentation of genes implicated in neurological and genetic disorders, including schizophrenia (19 genes in total;  $p = 9.08 \times 10^{-5}$ ) as well as cell death (table 3). These 19 significantly dysregulated genes altered by PCP were annotated by IPA as implicated in the etiology of schizophrenia: ATP1A3, ATP2B2, ATP6V1B2, CALR, DHPS, DPYSL2, EGR3, GABRB3, GRIA1, GRIK2, GSN, NEFL, PIK3R1, PLP1, PRKAR1A, RGS4, SNAP25, SOX5, and VDAC1. Pathways associated with PCP effects on PFC identified by canonical pathway analysis included a significant overrepresentation of genes implicated in calcium signaling and synaptic longterm potentiation (table 4). There was a 2.4-fold enrichment of genes from the PGC2 108 loci with PCP-dysregulated genes in the PFC (ATP2A2, GRIA1, MEF2C, PPP4C, and PTN).

Table 5. Using a set of	f 12 genes altered by (	OLZ, IPA canonica	l pathway analysis	identified the	following over-
represented canonical	pathways after correct	ting for multiple co	omparisons		

Ingenuity canonical pathways	B-H p value	Genes
Melatonin signaling	0.009	PRKACB, RORB, PRKCG, CAMK2G
Calcium signaling	0.009	PRKACB, MEF2C, ATP2A2, ATP2B2, CAMK2G
FYN receptor-mediated phagocytosis in macrophages and monocytes	0.009	PAK1, PLD3, ACTB, PRKCG
G protein-coupled receptor signaling	0.013	PRKACB, RGS4, RASA1, PRKCG, CAMK2G
Molecular mechanisms of cancer	0.013	PRKACB, PAK1, RHOB, RASA1, PRKCG, CAMK2G
B-H = Benjamini-Hochberg.		

## OLZ Effects on PFC Gene Expression

There were 12 genes with significantly differential expression in OLZ-administered animals compared to VEH controls, overlapping between both arrays (see online suppl. table 4). All 12 were upregulated in OLZ-administered subjects compared to controls. Canonical pathway analysis revealed overrepresentation of genes implicated in glutamate receptor signaling, ERK5 signaling, and calcium signaling (table 5). There was a 12.4-fold enrichment of genes from the PGC2 108 loci with OLZ-dysregulated genes in the PFC (NRGN, MEF2C).

## *Effects of OLZ Coadministration on PCP-Induced Changes in PFC Gene Expression*

There were a total of 85 genes with significantly differential expression in OLZ + PCP-administered animals compared to PCP alone, overlapping between both array platforms. Of these 85, 50 were normalized by OLZ + PCP, meaning that these genes fulfilled three criteria: (1) significantly dysregulated in PCP- versus VEH-administered animals, (2) significantly altered in the same direction between PCP- and PCP + OLZ-administered animals, and (3) showed no significant difference in expression between PCP + OLZ- and VEH-administered animals (see fig. 1-4 for the expression profiles of the representative genes). Because plasma levels for OLZ- and PCP-treated animals varied, we examined the correlation between individual plasma level and gene expression of the 50 OLZnormalized genes on both arrays. None of the 50 genes showed a significant correlation with gene expression and PCP or OLZ plasma levels on both arrays. IPA was used to functionally annotate the 50 genes normalized by OLZ administration (see tables 6, 7 for HU6800 and U95 results, respectively), which identified a significant overrepresentation of genes implicated in genetic disorders, including schizophrenia (7 genes: ATP1A3, ATP2B2, GABRB3, PLP1, RGS4, SNAP25 and VDAC1;  $p = 2.33 \times$  $10^{-2}$ ), neurological disorders, and cell death (tables 8, 9). Canonical pathway analysis revealed a significant overrepresentation of genes implicated in melatonin signaling, calcium signaling, FYN receptor-mediated phagocytosis in macrophages and monocytes, and G protein-coupled receptors (table 7). IPA was used to identify biological networks by querying interactions between genes stored in the Ingenuity Pathway Knowledge Base. IPA calculates a significance score for each network, which is the negative log of the p value associated with the network. IPA identified one gene network connecting 17 genes normalized by OLZ with a network score of 39 or a p value of  $10^{-39}$ . This network contained only genes downregulated by PCP and included ACTB, ATP2A2, ATP2B2, CAMK2G, GDI2, MAP2, NF2, PAK1, PRKACB, RAB3A, RAB6A, RASA1, RGS4, RHOB, SLC3A2, SNAP25, and SYN1. Two transcription factors, SOX5 and MEF, were identified by DAVID Bioinformatic Database to regulate a significant number of OLZ-reversed transcripts (see online suppl. tables 5, 6). There was a 2.8-fold enrichment of genes from the PGC2 108 loci with OLZ-normalized, PCP-dysregulated genes in the PFC (ATPA2, MEF2C).

# *Specificity of OLZ Effects on PCP-Induced Changes in PFC Gene Expression*

To test the specificity of PCP-induced gene expression changes reversed by the coadministration of OLZ, we also assessed the effects of AOLZ, AHAL, OLZ, and HAL on probe sets that were altered by PCP treatment and



**Fig. 1.** Representative gene RGS4 expression was reduced by PCP treatment and normalized by OLZ + PCP. Fold change is shown with respect to control levels.



**Fig. 3.** Representative gene RAB3A expression was reduced by PCP treatment and normalized by OLZ + PCP.

normalized by OLZ + PCP. The results are summarized in Venn diagrams (fig. 5, 6). Of the 50 genes normalized in OLZ + PCP-administered animals (fig. 5), only a small number was changed by AOLZ, OLZ, AHAL, or HAL administration: 2 genes were altered by AOLZ (MEF2C and CACNB4) and 1 gene by OLZ (MEF2C) (fig. 6), while 2 genes were altered by AHAL (CACNB4 and GAPDH) and 3 genes by HAL (CACNB4, GABRB3, and GAPDH).



**Fig. 2.** Representative gene NCAM expression was reduced by PCP treatment and normalized by OLZ + PCP.



**Fig. 4.** Representative gene SYN1 expression was reduced by PCP treatment and normalized by OLZ + PCP.

## Discussion

These are the first results of PCP and gene expression in a non-human primate model of schizophrenia. The results demonstrate that a large number of PCP-induced changes in gene expression are reversed by the administration of the antipsychotic OLZ. IPA was run using the list of 146 genes with PCP-induced expression alterations and showed an enrichment of genes previously implicat-

Table 6. PCP-altered genes were normalized by coadministration of OLZ and fulfilled three criteria: significantly dysregulated in PCP-
versus VEH-administered animals, significantly altered in the same direction between PCP- and PCP + OLZ-administered animals, and
showed no significant difference in expression between PCP+ OLZ- and VEH-administered animals

Gene	Gene title	PCP vs. VEH		PCP vs. PCP/OLZ		PCP/OLZ vs. VEH	
symbol		p value	FC	p value	FC	p value	FC
ACTB	actin, beta	4.5E-04	-1.24	3.3E-06	-1.36	8.8E-02	1.10
ACYP1	acylphosphatase 1, erythrocyte (common) type	3.0E-02	-1.16	5.0E-02	-1.15	8.4E-01	-1.01
ATP1A3	ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, alpha 3 polypeptide	8.0E-04	-1.22	5.5E-04	-1.23	8.4E-01	1.01
ATP2A2	ATPase, Ca <sup>++</sup> transporting, cardiac muscle, slow twitch 2	1.2E-02	-1.21	4.5E-02	-1.16	5.7E-01	-1.04
ATP2B2	ATPase, Ca <sup>++</sup> transporting, plasma membrane 2	1.4E-04	-1.28	6.3E-04	-1.25	6.5E-01	-1.03
ATP6V1A	ATPase, H <sup>+</sup> transporting, lysosomal 70 kDa, V1 subunit A	1.4E-03	-1.28	2.2E-02	-1.19	3.0E-01	-1.07
Clorf61	chromosome 1 open reading frame 61	9.2E-03	-1.19	3.6E-02	-1.15	5.8E-01	-1.03
CACNB4	calcium channel, voltage-dependent, beta 4 subunit	1.1E-03	-1.25	1.7E-02	-1.18	3.1E-01	-1.07
CAMK2G	calcium/calmodulin-dependent protein kinase II gamma	3.4E-02	-1.13	3.0E-02	-1.14	9.2E-01	1.01
CBX3 ///	chromobox homolog 3 (HP1 gamma homolog, <i>Drosophila</i> ) ///	2.2E-03	-1.24	6.4E-03	-1.21	7.2E-01	-1.02
LOC644101	similar to chromobox homolog					,	
CNTN1	Contactin 1	2.2E-05	-1.38	6.5E-04	-1.29	2.8E-01	-1.07
CSNK1G2	casein kinase 1. gamma 2	3.7E-02	-1.16	4.7E-02	-1.16	9.5E-01	-1.00
CTBP1	C-terminal-binding protein 1	5.9E-03	-1.22	2.7E-02	-1.18	5.5E-01	-1.04
CYP2A13	cytochrome P450 family 2 subfamily A polypeptide 13	4 3E-02	_1.14	4 6F-02	_1.14	1 0E+00	1.00
GABRB3	gamma-aminohutyric acid (GABA) A recentor heta 3	2.8E_04	_1.11	1.6E-02	_1.11	1.0E+00	_1.00
GADDH GADDH	glyceraldebyde 3 phosphate debydrogenase	5.2E.03	1 10	6 2E 05	1 32	1.4L-01	1 10
CDI2	CDD dissociation inhibitor 2	3.2E-03	-1.19	0.2E-03	-1.52	6 2E 01	1.10
GDI2 KCNIA D2	GDP dissociation minipilor 2	Z.4E-03	-1.21	9.7E-03	-1.10	0.2E-01	-1.05
KUNAB2	potassium voltage-gated channel, snaker-related subfamily, beta member 2	7.4E-03	-1.1/	9.3E-02	-1.10	2./E-01	-1.06
KLHDC3	keich domain containing 3	2.5E-03	-1.23	5.2E-03	-1.22	8.2E-01	-1.01
MAP2	microtubule-associated protein 2	1.1E-02	-1.24	3.0E-03	-1.30	5.7E-01	1.05
MATZA	methionine adenosyltransferase II, alpha	2.4E-02	-1.17	2.7E-02	-1.17	9.8E-01	-1.00
MBP	myelin basic protein	1.3E-03	-1.28	4.3E-02	-1.17	1.7E-01	-1.10
MEF2C	myocyte enhancer factor 2C	1.2E-03	-1.25	4.7E-03	-1.21	6.4E-01	-1.03
NF2	neurofibromin 2 (merlin)	4.7E-02	-1.13	1.7E-02	-1.17	6.1E-01	1.03
NOMO1 ///	NODAL modulator 1 /// NODAL modulator 2 /// NODAL modulator 3	1.3E-02	-1.15	1.7E-02	-1.15	9.6E-01	-1.00
NOMO2 ///							
NOMO3	1 11 11 . 1 1						
NRCAM	neuronal cell adhesion molecule	1.2E-03	-1.26	2.0E-02	-1.18	2.8E-01	-1.07
PAK1	p21 protein (Cdc42/Rac)-activated kinase 1	1.2E-03	-1.33	6.7E-03	-1.27	5.5E-01	-1.05
PLD3	phospholipase D family, member 3	1.1E-02	-1.19	6.5E-03	-1.21	7.9E-01	1.02
PLP1	proteolipid protein 1	7.6E-03	-1.21	9.3E-03	-1.21	9.7E-01	-1.00
PRKACB	protein kinase, cAMP-dependent, catalytic, beta	4.2E-03	-1.19	4.6E-03	-1.19	9.9E-01	1.00
PRKCG	protein kinase C, gamma	2.9E-03	-1.19	6.9E-04	-1.23	5.5E-01	1.03
PTPRS	protein tyrosine phosphatase, receptor type, S	2.6E-04	-1.28	1.6E-03	-1.24	5.6E-01	-1.04
RAB3A	RAB3A, member RAS oncogene family	3.4E-02	-1.15	2.8E-03	-1.23	2.9E-01	1.07
RAB6A	RAB6A, member RAS oncogene family	1.3E-03	-1.26	9.0E-03	-1.20	4.9E-01	-1.05
RASA1	RAS p21 protein activator (GTPase activating protein) 1	3.6E-02	-1.15	1.3E-02	-1.19	6.3E-01	1.03
RGS4	regulator of G-protein signaling 4	1.5E-04	-1.29	1.0E-04	-1.31	8.4E-01	1.01
RHOB	ras homolog gene family, member B	6.8E-03	-1.20	2.0E-02	-1.17	6.8E-01	-1.03
RORB	RAR-related orphan receptor B	5.1E-04	-1.31	1.0E-02	-1.22	2.8E-01	-1.08
RUNX1T1	runt-related transcription factor 1: translocated to, 1 (cyclin D-related)	4.7E-02	-1.14	6.0E-04	-1.27	7.8E-02	1.12
SFRS3	splicing factor, arginine/serine-rich 3	8.7E-03	-1.25	3.9E-02	-1.19	5.4E-01	-1.05
SLC3A2	solute carrier family 3 (activators of dibasic and neutral amino acid transport)	4 1E-02	-1.12	2.7E-02	-1.14	8.2E-01	1.01
SNAP25	sonare carrier raining 5 (activations of aboute and neutral annuo acta transport)	4.6E=03	_1.12	1.8E-02	_1.11	6.1E-01	-1.03
SVN1	synapcin I	7.2E_03	_1.22	5.4E-03	_1.10	8.7E-01	1.05
тнра	thuroid hormone recentor alpha (eruthroblastic leukemia viral	2 3E 02	1.10	7 OF 03	1.17	5.8E 01	1.01
111101	(v-erb-a) oncogen	2.51-02	-1.15	7.0L-05	-1.17	5.01-01	1.05
UBAP2L	ubiquitin-associated protein 2-like	3.7E-02	-1.16	4.5E-02	-1.15	9.5E-01	-1.00
UBE2D3	ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, veast)	3.8E-03	-1.25	2.5E-02	-1.19	4.6E-01	-1.05
UBE2S	ubiquitin-conjugating enzyme E2S	2.7E-02	-1.15	1.6E-02	-1.17	7.9E-01	1.02
VDAC1	voltage-dependent anion channel 1	1.0E-02	-1.15	2.2E-02	-1.14	7.7E-01	-1.02
YWHA7	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation	1.0E 02	_1.15	1 6F-02	_1.17	9.2F_01	1.02
1 TT 11/12/	protein, zeta pol	1.71-02	1.10	1.01-02	1.1/	7. <u>2</u> L-01	1.01
ZNF238	zinc finger protein 238	2.0E-02	-1.18	1.0E-02	-1.21	7.6E-01	1.02
	-						

The 50 normalized genes are shown that fulfilled three criteria on the U95 array. FC = Fold change.

Table 7. PCP-altered genes were normalized by coadministration of OLZ and fulfilled three critieria: significantly dysregulated in PCP-
versus VEH-administered animals, significantly altered in the same direction between PCP- and PCP + OLZ-administered animals, and
showed no significant difference in expression between PCP + OLZ- and VEH-administered animals

product         product         FC         product         FC         product         FC           ACTP         actinphosphatas 1, crythrocyte (common) type         5.54E-06         -1.29         1.06E-08         -1.12         9.66E-01         1.00           ATPLA         ATBacs, Na*K transporting, plan 3 polyceptide         9.48E-04         -1.18         8.75E-05         -1.12         9.66E-01         1.04           ATP12A         ATBacs, Ca*t transporting, plasma membrane 2         5.88E-04         -1.27         2.92E-03         -1.14         8.35E-06         -1.20         5.75E-01         -1.01           CACNB4         calcinum/calmodium/diperdependent brat 4 subunit         7.05E-07         -1.10         5.39F-06         -1.28         4.00E-02         -1.07           CACNB4         calcinum/calmodulim/dependent protein knase II gamma         2.70E-03         -1.13         6.30E-03         -1.18         1.17E-02         -1.16         6.40E-01         -1.00         CACNB4         6.40E-01         -1.01         CACNB4         6.40E-01         -1.10         5.40E-01         -1.10         6.40E-01         -1.10         6.40E-01         -1.10         6.40E-01         -1.02         CACNB4         6.40E-01         -1.02         CACNB4         6.40E-01         -1.02         CACNB4 <th>Gene</th> <th>Gene title</th> <th>PCP vs.VI</th> <th>EH</th> <th>PCP vs. Po</th> <th>CP/OLZ</th> <th>PCP/OLZ</th> <th>vs. VEH</th>	Gene	Gene title	PCP vs.VI	EH	PCP vs. Po	CP/OLZ	PCP/OLZ	vs. VEH
ACTB         actin. beta         5.54F.66         -1.29         1.06F.02         -1.12         3.81F.02         -1.12         9.66F.01         1.00           ATPAax, NATK' transporting, alpha 3 polypeptide         9.48F.04         -1.12         2.57F.03         -1.16         7.43F.01         1.04           ATP2AA         ATPaxe, Ca <sup>++</sup> transporting, plasma membrane 2         5.89F.04         -1.27         2.22F.03         -1.16         7.45F.01         1.01           ATPAS, Ca <sup>++</sup> transporting, plasma membrane 2         5.89F.04         -1.27         2.22F.03         -1.16         3.87F.06         -1.28         4.06F.02         -1.00           CACNE         Actium channel, volgeng-dependent, beta 4 subunit         7.64F.09         -1.01         3.97F.06         -1.28         4.06F.02         -1.09           CACNEX         calcium/almodulin-dependent protein kinase II gamma         2.0FE.03         -1.13         6.50F.03         -1.15         6.40F.01         -1.01           LOCAHU1         tailar to chromobx homolog         -1.01         3.2FE.03         -1.15         6.40F.01         -1.02           CARKIX         cammaba minobutyrin add (GABA) A receptor, heta 3         3.3EF.06         -1.17         5.8EF.03         -1.17         5.8FE.01         -1.00           CTPRA13	symbol		p value	FC	p value	FC	p value	FC
ACYP1         acyphospharse 1, crythrocyte (common) type         4.17E-02         -1.11         3.81E-02         -1.12         9.66E-01         1.00           ATP1AA         ATPase, Na"K transporting, plass membrane 2         1.07E-03         -1.18         8.275E-05         -1.23         4.07E-01         1.04           ATP2RA         ATPase, Ca" transporting, plass membrane 2         5.89E-04         -1.27         2.22E-03         -1.22         5.57E-01         1.04           ATPEVA         ATPase, Ca" transporting, plass membrane 2         5.89E-04         -1.03         3.89E-02         -1.16         3.89E-02         -1.16         3.89E-02         -1.16         8.46E-01         -1.01           CACKMCG         calcium channel, voltage-dependent rotice trians transman         2.70E-03         -1.13         6.30E-03         -1.12         2.34E-01         -1.01           CACKMCG         calcium channel, voltage-dependent rotice trians transman         3.02E-03         -1.15         9.64E-01         1.00           CACKMCG         calcium channel, voltage-dependent rotice triansman         3.02E-03         -1.12         2.04E-01         1.00           CACKMCG         calcium channel, voltage-dependent rotice triansman         3.02E-03         -1.12         2.04E-01         -1.00         0.02E         0.02E-01	ACTB	actin, beta	5.54E-06	-1.29	1.06E-08	-1.42	4.61E-02	1.10
ATP1A3       ATPaxe, Na <sup>1</sup> (K <sup>+</sup> transporting, alpha's polypeptide       9.48E-04       -1.18       8.275E-03       -1.16       7.45E-01       -1.01         ATP2A3       ATPaxe, Ca <sup>++</sup> transporting, plasma membrane 2       5.89E-04       -1.27       2.22E-03       -1.16       3.84E-01       -1.01         ATP2A3       ATPaxe, Ca <sup>++</sup> transporting, plasma membrane 2       5.89E-04       -1.02       3.97E-06       -1.24       8.34E-01       -1.01         Clorfiel       chromosome 1 open reading frame 61       2.39E-02       -1.16       3.97E-06       -1.12       8.34E-01       -1.01         CACMR4       calcium clanmodulin-dependent protein kinase II gamma       2.07E-03       -1.13       6.50E-03       -1.12       7.32E-01       -1.01         CACMI4C       calcium clanmodulin-dependent protein kinase II gamma       2.07E-03       -1.17       5.04E-0       -1.02         CSNIM (C       cascin kinase I, gamma 2       -1.16E-02       -1.15       5.40E-0       -1.00         CSNIM (C       cascin kinase I, gamma 2       -1.02       3.38E-06       -1.32       2.10E-04       -1.27       5.40E-01       -1.02         CSNIM (C       cascin kinase I, gamma 2       -1.16       5.40E-01       -1.02       2.40E-01       -1.02       -1.02       -1.02	ACYP1	acylphosphatase 1, erythrocyte (common) type	4.17E-02	-1.11	3.81E-02	-1.12	9.66E-01	1.00
ATP28a       ATPses, Ca** transporting, plasma membrane 2       1.07E-03       -1.18       2.37E-04       -1.27       2.92E-03       -1.22       5.37E-01       1.04         ATP2BA       ATPses, Ca** transporting, plasma membrane 2       3.08E-04       -1.27       2.92E-03       -1.62       5.37E-01       1.04         ATPEVA       ATPses, Ca** transporting, plasma membrane 2       7.08E-02       -1.61       3.89E-02       -1.16       6.30E-02       -1.61       6.30E-02       -1.61       6.30E-02       -1.61       6.30E-02       -1.02         CACKNK       calcium channel, voltage-dependent rotes thase It gamma homolog, <i>Drosophila</i> ) ///       3.59E-02       -1.14       2.31E-02       -1.16       8.46E-01       -1.01         CANKA       calcium channel, voltage-dependent rotes thase It gamma homolog, <i>Drosophila</i> ) ///       3.59E-02       -1.17       2.30E-03       -1.15       9.64D-0       -1.02         CNNIC1       cass in knase I, gamma 2       .50E-03       -1.18       2.31E-04       -1.01       0.00	ATP1A3	ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, alpha 3 polypeptide	9.48E-04	-1.18	8.75E-05	-1.23	4.07E-01	1.04
ATP28       ATP3es, C4" transporting, Jassama membrane 2       5.89E-04       -1.27       2.92E-03       -1.22       5.57E-01       1.04         ATPVIA       ATPse, H" transporting, Jassama Tobla, V1 subunit       3.35E-07       -1.63       3.85E-07       -1.14       8.34E-00       -1.09         CAMKG       calcium/calmodulin-dependent protein kinase II gamma       2.70E-03       -1.13       6.50E-03       -1.12       7.32E-01       -1.01         CAMKG       calcium/calmodulin-dependent protein kinase II gamma       2.70E-03       -1.13       6.50E-03       -1.12       6.40E-01       -1.02         CXNNL       catasin kinase I, gamma 2       1.16E-02       -1.15       6.40E-01       -1.02         CXNNL       catasin kinase I, gamma 2       1.16E-02       -1.15       6.46E-01       -1.00         CXNNL       catasin kinase I, gamma 2       1.16E-02       -1.13       5.05E-03       -1.12       6.46E-01       -1.00         CXNNL       catasin kinase I, gamma 2       1.16E-02       -1.13       5.04E-01       -1.02       6.71E-03       -1.14       6.34E-01       -1.01         CNNL       catasin kinase I, gamma 2       1.06E-03       -1.12       6.44E-04       -1.12       6.44E-04       -1.12       6.44E-04       -1.12	ATP2A2	ATPase, Ca <sup>++</sup> transporting, cardiac muscle, slow twitch 2	1.07E-03	-1.18	2.57E-03	-1.16	7.45E-01	-1.01
ATPVIA       ATPse, H* transporting, lysosomal 70 kDa, V1 subunit A       3.35E 07       -1.41       8.34E-01       1.01         CACNM       calcium channel, voltage-dependent, beta 4 subunit       7.64E-09       -1.40       8.39F-02       -1.14       8.34E-01       -1.01         CACNMS       calcium/calmodulin-dependent protein kinase II gamma       2.70E-03       -1.13       6.50E-03       -1.12       7.32E-04       -1.01       7.32E-04       -1.10       8.46E-01       -1.01         CANX1       calcium/calmodulin-dependent protein kinase II gamma       3.62E-03       -1.18       1.77E-03       -1.15       9.46E-01       -0.02         CNN11       contactin 1       5.07E-03       -1.17       5.98E-03       -1.17       9.99E-01       -1.00         CXP2A13       cytochrome P450, fonghyta chytylogenase       1.80E-02       -1.13       2.10E-03       -1.17       9.99E-01       -1.00         GADBB       gymma-aminobutyria cald (GABA) A receptor, beta 3       3.38E-06       -1.32       8.44E-04       -1.02       -1.02       -1.12       9.42E-0       -1.10       9.46E-01       -1.02       -1.02       -1.02       -1.02       -1.02       -1.02       -1.02       -1.02       -1.12       -4.24E-07       -1.21       -4.24E-07       -1.12	ATP2B2	ATPase, Ca <sup>++</sup> transporting, plasma membrane 2	5.89E-04	-1.27	2.92E-03	-1.22	5.57E-01	1.04
Chorfiol         chromosome 1 open reading frame 61         2.39F-02         -1.14         8.325F-01         -1.01           CACMNG         calcium channel, voltage-dependent, bet 4 subunit         7.04E-03         -1.13         6.50E-03         -1.12         7.32E-01         -1.01           CAMK2G         calcium/calimodulin-dependent protein kinase II gamma         2.70E-03         -1.13         6.50E-03         -1.12         7.32E-01         -1.01           LOCAH101         similar to chromobox homolog.         3.62E-03         -1.15         9.40E-01         -1.00           CNTN1         contactin 1         3.62E-03         -1.15         9.40E-01         -1.00           CNTR1         contactin 1         3.62E-03         -1.15         9.40E-01         -1.00           CABR3         gamma-animobutyric acid (GABA) receptor, beta 3         3.38E-06         -1.2         4.46E-04         -1.2         6.46E-0         -1.00           CABR3         gamma-animobutyric acid (GABA) receptor, beta 3         3.38E-06         -1.2         4.46E-0         -1.01         6.36E-01         -1.02           CABR3         gamma-animobutyric acid (GABA) receptor, beta 3         3.36E-06         -1.27         8.47E-04         -1.28         5.44E-0         -1.11         6.56E-01         -1.02 <td>ATP6V1A</td> <td>ATPase, H<sup>+</sup> transporting, lysosomal 70 kDa, V1 subunit A</td> <td>3.35E-07</td> <td>-1.39</td> <td>1.76E-07</td> <td>-1.41</td> <td>8.34E-01</td> <td>1.01</td>	ATP6V1A	ATPase, H <sup>+</sup> transporting, lysosomal 70 kDa, V1 subunit A	3.35E-07	-1.39	1.76E-07	-1.41	8.34E-01	1.01
CACNR         calcium channel, voltage-dependent, brat 4 subunit         7.64E.09         -1.40         3.59E.06         -1.38         4.60E.02         -1.00           CANKGG         calcium/calmodulin-dependent protein kinase II gamma         2.70F.03         -1.11         5.50F.03         -1.12         7.32E.04         1.00           CRN101         contactin 1         3.62F.03         -1.18         1.17F.02         -1.15         9.64E.01         1.00           CRN101         contactin 1         5.07F.03         -1.17         5.98E.03         -1.17         9.99E.01         -1.00           CRN102         costen kinase L gamma 2         1.16E.02         -1.13         2.00F.04         -1.12         9.99E.01         -1.00           GADBM         gyneraldehyde-3.piophat dehydrogenase         1.80E.02         -1.13         2.10F.04         -1.24         6.48F.04         -1.02         0.61E         -1.24         6.34F.01         -1.01         0.62E         -1.24         6.34F.01         -1.02         0.61E         0.102         0.11E         0.61E         0.122         0.61E         0.122	Clorf61	chromosome 1 open reading frame 61	2.39E-02	-1.16	3.89E-02	-1.14	8.25E-01	-1.01
CAMK2C         calcium/calmodulin-dependent protein kinase II gamma         2.70E-03         -1.14         6.50E-03         -1.12         7.32E-01         -1.01           CRX3//r         Chromobox homolog         359E-02         -1.14         2.34E-02         -1.16         8.46E-01         1.01           CXCNTN1         contactin 1         359E-02         -1.18         1.17E-02         -1.15         6.46E-01         1.00           CTRP1         C-terminal binding protein 1         2.92E-03         -1.12         5.82E-03         -1.13         8.57E-01         -1.01           GABRB3         gamma-animobutyric aid (GABA) A receptor, beta 3         3.38E-06         -1.32         8.44E-04         -1.20         6.46E-01         -1.02           GADR3         gamma-animobutyric aid (GABA) A receptor, beta 3         3.38E-06         -1.33         5.96E-04         -1.24         6.34E-01         -1.02           bata member 2         -         -         -1.27         8.47E-04         -1.10         6.96E-01         -1.02           MAP2         methoinin containing 3         2.64E-04         -1.23         8.44E-04         -1.33         5.96E-04         -1.24         .24E-01         -1.02           MAP2         methoinin a danoshitania containing 3         2.64E-03	CACNB4	calcium channel, voltage-dependent, beta 4 subunit	7.64E-09	-1.40	3.97E-06	-1.28	4.60E-02	-1.09
CBX3///         chromobox homolog 3 (HPI gamma homolog, Drosophila) ///         3.59E-02         -1.14         2.34E-02         -1.16         8.46E-01         1.01           LOC44101         similar to chromobox homolog         3.62E-03         -1.18         9.22E-03         -1.15         9.22E-03         -1.15         9.22E-03         -1.17         9.92E-01         -1.02           CNTNIC         costs kinase 1, gamma 2         1.01         5.07E-03         -1.17         4.30E-02         -1.18         8.22E-03         -1.17         4.30E-04         -1.20         6.71E-02         -1.10         6.72E-01         -1.00         7.72E-01         -1.00           CNADE         page aget channel, shaker-related subfamily, beta member 2         2.04E-04         -1.23         3.72E-01         -1.00           MAP2         microbuble-associated protein 2         1.60E-03         -1.25         9.27E-01         -1.00	CAMK2G	calcium/calmodulin-dependent protein kinase II gamma	2.70E-03	-1.13	6.50E-03	-1.12	7.32E-01	-1.01
LOC64101         similar to chromobox homolog.         5.62E-03         -1.18         1.17E-02         -1.15         6.40E-01         -1.02           CSNNIC         caserin kinase 1, gamma 2         1.16E-02         -1.18         9.82E-03         -1.15         9.46E-01         1.00           CTPBP1         C-terminal binding protein 1         5.07E-03         -1.27         5.82E-03         -1.12         9.46E-01         1.00           CYP2A13         cytochrome P450, family 2, subfamily A, polypeptide 13         2.92E-02         -1.12         8.44E-04         -1.20         6.71E-02         -1.10           GABRB3         gamma-aninobutyric acid (GABA) A receptor, heta 3         3.38E-06         -1.31         1.20E-02         -1.12         9.46E-01         -1.02           GADP         Defasiocation inhibitor 2         2.02E-04         -1.27         8.47E-04         -1.28         4.24E-07         -1.39         3.78E-02         -1.10           KCHDC3         keld-domain containing 3         2.64E-04         -1.26         7.90E-05         -1.27         9.47E-01         1.06           MF2D         metrotubule-associated protein 2         1.46E-02         -1.18         1.10E-03         -1.18         7.45E-01         1.00           MF2D         metrotbule-associated prote	CBX3 ///	chromobox homolog 3 (HP1 gamma homolog, Drosophila) ///	3.59E-02	-1.14	2.34E-02	-1.16	8.46E-01	1.01
CMTNI         contactin I         3.62E-03         -1.18         1.17E-02         -1.17E         6.40E-01         1.02           CTBPI         C-terminal binding protein I         5.07E-03         -1.17         9.42E-03         -1.17         9.49E-01         1.00           CTP211         Cyteroherme P450, family 2, subfamily A, polypeptide 13         2.92E-02         -1.12         4.30E-02         -1.12         4.30E-01         -1.12         6.71E-02         -1.10         6.71E-02         -1.10         6.71E-02         -1.10         6.71E-02         -1.10         6.71E-02         -1.10         6.71E-02         -1.10         6.70E-01         -1.00           CNADSU         postesium voltage-gated channel, shaker-related subfamily, relation relatin relation relation relation relatin relation relation relatin rel	LOC644101	similar to chromobox homolog						
CSNK162         casein kinase 1, gamma 2         1.167-02         -1.15         9.82E-03         -1.15         9.94E-01         1.00           CTBPI         C-terminal binking protein 1         5.07E-03         -1.17         5.08E-03         -1.11         8.57E-01         -1.01           CABRBA3         gamma-aminobutyric acid (GABA) A receptor, beta 3         3.38E-06         -1.32         8.44E-04         -1.20         6.71E-02         -1.10           GAPDH         glyceraldehyde-3-phosphate dehydrogenase         1.80E-02         -1.13         1.84E-02         -1.14         6.94E-01         -1.00           beta member 2         camember 2         1.13         1.84E-02         -1.11         6.94E-01         -1.02           MAP2         methionine adenosyltransferase II, alpha         6.02E-05         -1.26         7.90E-06         -1.25         9.27E-01         -1.00           MEP2         mycytre enhancer factor 2C         3.59E-03         -1.18         7.45E-01         1.01           MEP2         mycytre enhancer factor 2C         3.59E-03         -1.26         7.90E-03         -1.25         9.27E-01         -1.00           MEP2         mycytre enhancer factor 2C         3.59E-03         -1.18         7.45E-01         1.00           NOAO1 /// M	CNTN1	contactin 1	3.62E-03	-1.18	1.17E-02	-1.15	6.40E-01	-1.02
CTBP1         C-terminal binding protein 1         5.07E-03         -1.17         9.99E-01         -1.07           GAPDIA         gycarcheory 450, family 2, subfamily A, polypeptide 13         2.02E-02         -1.11         8.57E-01         -1.01           GAPDIA         gycarchedyde-3-phosphate debydrogenase         1.807-02         -1.13         2.04E-04         -1.20         6.71E-02         -1.10           GDI2         GDP dissociation inhibitor 2         2.20E-04         -1.23         8.47E-04         -1.24         6.34E-01         -1.03           KCNA82         portasium voltage-grade channel, shaker-related subfamily, beta member 2         -1.13         1.84E-02         -1.14         6.34E-01         -1.03           MAP2         microtubule associated protein 2         1.60E-03         -1.33         5.96E-04         -1.27         7.20E-01         1.00           MAP2         microtubule associated protein 2         1.60E-03         -1.34         5.96E-04         -1.27         7.20E-01         1.00           MP2         methionine adenosyltransferase II, alpha         6.02E-05         -1.12         2.12E-04         -1.29         3.78E-02         1.12           MOM2         Minoudulator 1/// NODAL modulator 2/// NODAL         2.18E-03         -1.18         2.12E-04         -1.29	CSNK1G2	casein kinase 1, gamma 2	1.16E-02	-1.15	9.82E-03	-1.15	9.46E-01	1.00
CYP2A13       cytochrome P450, family 2, subfamily A, polypeptide 13       2.92E-02       -1.11       4.30E-02       -1.11       8.57E-01       -1.01         GABRB3       gamma-aninobutyric acid (GABA) A receptor, beta 3       3.38E-06       -1.32       8.44E-04       -1.20       6.4E-01       -1.00         GAPDH       glyceraldehyde-3-phosphate dehydrogenase       1.80E-02       -1.13       1.84E-02       -1.11       6.96E-01       -1.02         beta       member 2       kelch domain containing 3       2.64E-04       -1.25       4.24E-07       -1.39       3.78E-02       1.12         MAP2       microtubule-associated protein 2       1.60E-03       -1.16       7.90E-04       -1.27       7.20E-01       1.00         MF2C       mycyctre enhancer factor 2C       3.59E-04       -1.27       7.20E-01       1.00         MF2C       mycyctre enhancer factor 2C       3.59E-03       -1.18       2.74E-01       1.00         NF2C       mycyctre enhancer factor 2C       3.59E-03       -1.12       2.12E-04       -1.29       3.07E-01       1.06         NF2C       mycyctre enhancer factor 2C       3.59E-04       -1.24       7.69E-03       -1.19       5.36E-01       1.06         NF2C       mycyctre enhancer factor 2C       3	CTBP1	C-terminal binding protein 1	5.07E-03	-1.17	5.08E-03	-1.17	9.99E-01	-1.00
GABRB       gamma-minobutyric acid (GABA) A receptor, beta 3       3.38E-06       -1.22       8.44E-04       -1.20       6.71E-02       -1.10         GADDH       gyceraldedyde-phydrogenase       1.80E-02       -1.13       2.10E-02       -1.12       9.46E-01       -1.00         GDU       GDP dissociation inhibitor 2       2.20E-04       -1.27       8.47E-04       -1.24       6.54E-01       -1.02         beta member 2       Etch domain containing 3       2.64E-04       -1.25       4.24E-07       -1.39       3.78E-02       1.12         MAP2       microtubule-associated protein 2       1.60E-03       -1.26       7.90E-04       -1.27       9.47E-04       -1.00         MAT2A       methionine adenosyltransferase II, alpha       6.02E-05       -1.26       7.90E-04       -1.18       7.45E-01       1.01         MEP2       mycotyte enhancer factor 2C       3.39E-03       -1.18       2.16E-03       -1.18       2.06E-03       -1.28       7.00E-03       -1.28       7.00E-01       1.06         NOMO2 ///       modulator 1       NODAL modulator 2 /// NODAL       2.19E-03       -1.18       2.01E-03       -1.18       2.01E-03       -1.18       2.01E-03       -1.12       2.06E-03       -1.27       2.65E-01       -1.06 <td>CYP2A13</td> <td>cytochrome P450, family 2, subfamily A, polypeptide 13</td> <td>2.92E-02</td> <td>-1.12</td> <td>4.30E-02</td> <td>-1.11</td> <td>8.57E-01</td> <td>-1.01</td>	CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	2.92E-02	-1.12	4.30E-02	-1.11	8.57E-01	-1.01
GAPDH         glyceraldehyde-3-phosphate dehydrogenase         1.80E-02         -1.13         2.10E-02         -1.12         9.46E-01         -1.03           KCNAB2         potassium voltage-gated channel, shaker-related subfamily, bet amember 2         7.22E-03         -1.13         1.84E-02         -1.13         1.84E-02         -1.13         1.84E-02         -1.11         6.96E-01         -1.02           KLHDC3         kelch domain containing 3         2.64E-04         -1.25         4.24E-07         -1.35         5.96E-04         -1.77         7.20E-01         1.03           MAP2         methionine adenosyltransferase II, alpha         6.02E-05         -1.26         7.90E-05         -1.25         9.27E-01         -1.00           MBP         mycicit basic protein         2.34E-03         -1.12         2.12E-04         -1.29         3.07E-01         1.06           NDC1/I/         NDAL         colustor 1//NODAL         NDAL         2.19E-03         -1.18         2.16E-03         -1.18         9.97E-01         1.00           NOMO3/I/         NDOAL         colustor 1//NODAL         2.19E-03         -1.18         2.20E-05         -1.00         NRCAM         protein kinase, CAPR-dependent, catalytic, beta         4.72E         4.66E-03         -1.12         9.97E-01         1.00	GABRB3	gamma-aminobutyric acid (GABA) A receptor, beta 3	3.38E-06	-1.32	8.44E-04	-1.20	6.71E-02	-1.10
GDI2         GDP dissociation inhibitor 2         2.20E-04         -1.27         8.47E-04         -1.24         6.34E-01         -1.03           KCNAB2         potassium voltange-gated channel, shaker-related subfamily, beta member 2         2.44E-04         -1.25         4.24E-07         -1.39         5.78E-02         1.12           MAP2         microtubule-associated protein 2         1.60E-03         -1.33         5.96E-04         -1.27         2.72E-01         -1.00           MBP         mycorite enhancer factor 2C         3.59E-03         -1.16         1.19E-03         -1.18         7.43E-01         1.01           MEP2         metrofibromine adenosyltransferase II, alpha         6.02E-05         -1.20         3.07E-01         1.06           MEP2         meyocyte enhancer factor 2C         3.59E-03         -1.18         2.16E-03         -1.18         2.16E-03         -1.18         9.97E-01         1.00           NOM02 /// Moddlator 3         NOM02 /// Moddlator 3         -1.04         1.02E-04         -1.22         9.67E-03         -1.18         2.65E-01         -1.06           PAK1         p21 protein in 0         1.5E-03         -1.18         2.66E-03         -1.14         7.26E-01         -1.00           PLP3         protein kinase, CAMP-dependent, catalytic	GAPDH	glyceraldehyde-3-phosphate dehydrogenase	1.80E-02	-1.13	2.10E-02	-1.12	9.46E-01	-1.00
KCNAB2         potassium voltage-gated channel, shaker-related subfamily,         7.22E-03         -1.13         1.84E-02         -1.11         6.96E-01         -1.02           beta member 2         1.00         -1.25         4.24E-07         -1.39         3.78E-02         1.12           MAP2         incrotubule-associated protein 2         1.60E-03         -1.26         7.90E-05         -1.27         7.20E-01         1.03           MAT2A         methionine adenosyltransferase II, alpha         6.02E-05         -1.26         7.90E-05         -1.27         7.00E-01         1.06           MEP2         mycoyte enhancer factor 2C         3.59E-03         -1.12         2.12E-04         -1.29         3.07E-01         1.06           NOMO1///         NODAL         2.19E-03         -1.18         7.45E-01         1.04           NOMO2///         modulator 1/// NODAL modulator 2/// NODAL         2.19E-03         -1.18         3.20E-05         -1.12         9.37E-01         1.06           NOMO3         /// MODAL modulator 3         // NODAL         2.19E-03         -1.18         3.20E-05         -1.27         2.65E-01         -1.04           NOMO3         // NODAL modulator 3         // NODAL         1.05E-06         -1.12         9.47E-01         1.00	GDI2	GDP dissociation inhibitor 2	2.20E-04	-1.27	8.47E-04	-1.24	6.34E-01	-1.03
beta member 2         containing 3         2.64E-04         -1.25         4.24E-07         -1.39         3.78E-02         1.12           MAP2         microtubule-associated protein 2         1.60E-03         -1.33         5.96E-04         -1.27         7.20E-01         1.03           MAT2A         methonine adenosyltransferase II, alpha         6.02E-05         -1.26         7.27E-01         -1.00           MBP         myelin basic protein         2.84E-03         -1.16         1.19E-03         -1.18         7.45E-01         1.06           NF2         neurofibromin 2 (merlin)         1.54E-03         -1.24         7.06E-03         -1.19         5.36E-01         -1.04           NOMO2 /// NOMO2 /// NODAL modulator 3	KCNAB2	potassium voltage-gated channel, shaker-related subfamily,	7.22E-03	-1.13	1.84E-02	-1.11	6.96E-01	-1.02
KLHD.25       kelch domain containing 3       2.644-94       -1.25       4.44-17       -1.39       3.748-02       1.12         MAP2       methionine adenosyltransferase II, alpha       6.02E-05       -1.26       7.90E-05       -1.25       9.27E-01       1.00         MEP       myelin basic protein       2.84E-03       -1.16       1.19E-03       -1.18       7.45E-01       1.01         MEP       myocyte enhancer factor 2C       3.59E-03       -1.21       2.12E-04       -1.29       3.07E-01       1.06         NDOMO1 /// NODAL       neurofibromin 2 (merlin)       1.54E-03       -1.18       2.16E-03       -1.18       9.97E-01       1.00         NOMO2 /// modulator 3       NOMO3       -1.22       9.67E-03       -1.27       2.65E-01       -1.06         PLO3       phospholipase D family, member 3       1.21E-03       -1.15       2.60E-03       -1.17       2.25E-01       -1.06         PLO3       phospholipase D family, member 3       1.21E-03       -1.15       2.60E-03       -1.17       2.82E-01       -1.01         PLO4       protein kinase, CAMP-dependent, catalytic, beta       4.72E-08       -1.36       7.16E       8.25E-01       1.03         PRKACB       protein kinase, CAMP-dependent, catalytic, beta	<u>ELLID CA</u>	beta member 2	0 ( I E 0 I	1.05	1.2.45	1.20	2 505 02	1.10
MAP2       microtubule-associated protein 2       1.60E-03       -1.35       5.96E-04       -1.37       7.20E-01       1.100         MAT2A       methionine adenosyltransfersa II, alpha       6.02E-05       -1.26       7.92E-01       1.101         MEPC       myocyte enhancer factor 2C       3.59E-03       -1.21       2.12E-04       -1.29       3.07E-01       1.06         NOM02 ///       modulator 3       -1.18       2.16E-03       -1.18       9.97E-01       1.00         NOM023       modulator 3       -1.18       2.16E-03       -1.18       9.97E-01       1.06         NOM03       modulator 3       -1.16       2.16E-03       -1.17       2.65E-01       -1.06         PLN       poteoling topticin (Cdc42/Rac)-activated kinase 1       4.56E-04       -1.22       9.67E-03       -1.17       2.65E-01       -1.06         PLN       proteoling topticin 1       1.25E-02       -1.12       1.06E-03       -1.14       7.76E-01       -1.01         PRKCAB       protein kinase, cAMP-dependent, catalytic, beta       4.72E-08       -1.36       7.16E-08       -1.35       8.92E-01       -1.01         PRKCCB       protein kinase, cAMP-dependent, catalytic, beta       4.72E-08       -1.36       6.716E-08       -1.26	KLHDC3	kelch domain containing 3	2.64E-04	-1.25	4.24E-07	-1.39	3.78E-02	1.12
MA12A       methionine adenosyltransferase it, appa       6.020-09       -1.26       -9.02-09       -1.25       9.02-101       -1.10         MBP       myelin basic protein       2.84E-03       -1.16       1.19E-03       -1.18       7.45E-01       1.01         MEPZ       meurofibromin 2 (merlin)       1.54E-03       -1.24       7.69E-03       -1.19       5.36E-01       -1.04         NOMO2 ///       modulator 1 /// NODAL modulator 2 /// NODAL       2.19E-03       -1.18       2.16E-03       -1.18       9.97E-01       1.00         NOMO3       meuronal cell adhesion molecule       1.05E-06       -1.34       3.20E-05       -1.27       2.65E-01       -1.06         PLD3       phospholipase D family, member 3       1.21E-03       -1.15       2.60E-03       -1.14       7.76E-01       -1.01         PKAC       protein (Cdc42/Rac)-activated kinase 1       1.25E-02       -1.12       1.06E-02       -1.12       9.47E-01       1.00         PKACG       protein kinase, C AMP-dependent, catalytic, beta       4.72E-08       -1.34       7.16E-08       -1.33       8.92E-01       -1.01         PKKCG       protein kinase, C gamma       2.15E-03       -1.17       1.28E-05       -1.26       8.4E-02       1.08         RAB6	MAP2	microtubule-associated protein 2	1.60E-03	-1.33	5.96E-04	-1.37	7.20E-01	1.03
MBP         Injendasic protein         2.84E-03         -1.16         1.19E-03         -1.18         7.48E-01         1.01           MEF2C         moyorge enhancer factor 2C         3.59E-03         -1.24         2.12E-04         -1.29         3.07E-01         1.06           NF2         neurofibromin 2 (merlin)         1.54E-03         -1.24         2.0EE-03         -1.18         9.97E-01         1.00           NOMO1 ///         MODAL modulator 1 /// NODAL         2.19E-03         -1.18         2.0EE-03         -1.18         9.97E-01         1.00           NOMO3         muronal cell adhesion molecule         1.05E-06         -1.34         3.20E-05         -1.27         2.65E-01         -1.06           PAK1         p21 protein (Cdc42/Rac)-activated kinase 1         4.56E-04         -1.22         9.67E-03         -1.17         2.8E-01         -1.01           PLP1         proteolipid protein 1         1.21E-03         -1.12         1.06E-02         -1.12         9.47E-01         1.00           PKKCG         protein kinase, cAMP-dependent, catalytic, beta         4.72E-08         -1.36         7.16E-08         -1.35         8.92E-01         -1.01           PKKCG         protein kinase, C gamma         2.15E-03         -1.22         6.67E-04         -	MAIZA	methionine adenosyltransferase II, alpha	6.02E-05	-1.26	7.90E-05	-1.25	9.2/E-01	-1.00
MIF2C       myocyte ennancer factor 2C       3-39-E-03       -1.21       2.12E-04       -1.29       3.07E-01       1.106         NF2       neurofibromin 2 (merlin)       1.54E-03       -1.18       2.16E-03       -1.18       9.97E-01       1.00         NOMO2 ///       modulator 3       nodulator 3       nodulator 3       9.97E-01       1.00         NOMO3       neuronal cell adhesion molecule       1.05E-06       -1.34       3.20E-05       -1.27       2.65E-01       -1.06         PAK1       p21 protein (Cdc42/Rac)-activated kinase 1       4.56E-04       -1.22       9.67E-03       -1.12       2.35E-01       -1.01         PLP1       protein kinase, cAMP-dependent, catalytic, beta       4.72E-08       -1.16       7.16E-08       -1.35       8.32E-01       -1.01         PRKACB       protein kinase, cAMP-dependent, catalytic, beta       4.72E-03       -1.17       1.28E-05       -1.26       8.14E-02       1.08         PTPRS       protein kinase, Cagamma       2.15E-03       -1.17       1.28E-04       -1.18       7.35E-02       -1.00         RAB3A, member RAS oncogene family       7.58E-05       -1.21       6.88E-04       -1.18       7.35E-02       -1.08         RASA1       RAB3DA, member RAS oncogene family <td< td=""><td>MBP</td><td>myelin basic protein</td><td>2.84E-03</td><td>-1.16</td><td>1.19E-03</td><td>-1.18</td><td>7.45E-01</td><td>1.01</td></td<>	MBP	myelin basic protein	2.84E-03	-1.16	1.19E-03	-1.18	7.45E-01	1.01
NP2         neuronitoromin 2 (merrin)         1.394-03         -1.24         7.694-03         -1.19         5.36E-01         -1.04           NOMOU /// NOMO2         modulator 1 /// NODAL modulator 2 /// NODAL         2.19E-03         -1.18         2.16E-03         -1.18         9.97E-01         1.00           NOMO3         neuronal cell adhesion molecule         1.05E-06         -1.34         3.20E-05         -1.27         2.65E-01         -1.06           PAK1         p21 protein (Cdc42/Rac)-activated kinase 1         4.56E-04         -1.22         9.67E-03         -1.14         7.76E-01         -1.01           PLD3         phospholipase D family, member 3         1.12E-03         -1.12         1.06E-02         -1.22         9.47E-01         1.00           PRKACB         protein kinase, C, gamma         2.15E-03         -1.17         1.28E-05         -1.26         8.14E-02         1.08           PTPRS         protein kinase, C, gamma         2.15E-03         -1.21         1.66E-04         -1.26         6.28E-01         1.03           RAB3A         RAB6A, member RAS oncogene family         7.58E-05         -1.21         3.18E-07         -1.30         7.74E-02         1.08           RGS4         regulator of G-protein singining 4         8.76E-07         -1.31	MEF2C	myocyte enhancer factor 2C	3.59E-03	-1.21	2.12E-04	-1.29	3.0/E-01	1.06
NOMO2 ///       NODAL includator 2 /// NODAL includator 2 /// NODAL       2.19E-03       -1.18       9.97E-01       1.00         NOMO2 ///       modulator 3         NOMO2 //       modulator 3         NRCAM       neuronal cell adhesion molecule       1.05E-06       -1.14       3.20E-05       -1.27       2.65E-01       -1.06         PLN1       phospholipase D family, member 3       1.21E-03       -1.15       2.60E-03       -1.14       7.76E-01       -1.01         PRKACB       protein kinase, CAMP-dependent, catalytic, beta       4.72E-08       -1.36       7.16E-08       -1.35       8.92E-01       -1.01         PRKACB       protein kinase, CAMP-dependent, catalytic, beta       4.72E-08       -1.36       7.16E-08       -1.26       0.28E-01       -1.01         PRKACG       protein kinase, receptor type, S       2.50E-03       -1.17       1.28E-05       -1.26       8.48E-04       -1.26       0.28E-01       1.03         RABAA       RAB3A       RAB5A       member RAS oncogene family       7.58E-05       -1.21       3.18E-07       -1.30       7.74E-02       1.08         RASA1       RAS p21 protein activator (GTPase activating protein) 1       1.26E-03       -1.31       1.51E-07       -1.34       5.67E-01       1.03	NF2 NOMO1 ///	NODAL medulator 1 /// NODAL medulator 2 /// NODAL	1.54E-03	-1.24	7.69E-03	-1.19	5.36E-01	-1.04
NOMOS         Instruction of Section 1         Instruction 1         Instr	NOMO2 ///	modulator 3	2.19E-05	-1.18	2.10E-03	-1.18	9.9/E-01	1.00
NORGO         neuronal cell adhesion molecule         1.05E-06         -1.34         3.20E-05         -1.27         2.65E-01         -1.06           PAK1         p21 protein (Cdc42/Rac)-activated kinase 1         4.56E-04         -1.22         9.67E-03         -1.15         2.53E-01         -1.06           PLD3         phospholipase D family, member 3         1.21E-03         -1.15         2.60E-03         -1.14         7.76E-01         -1.01           PRKCG         protein kinase, cAMP-dependent, catalytic, beta         4.72E-08         -1.36         7.16E-08         -1.35         8.92E-01         -1.01           PRKCG         protein kinase, C. gamma         2.15E-03         -1.17         1.28E-05         -1.26         6.14E-02         1.08           PRKCG         protein kinase, coceptor type, S         2.50E-03         -1.23         6.67E-04         -1.26         6.28E-01         1.03           RAB6A         RAB6A, member RAS oncogene family         3.21E-06         -1.21         3.18E-07         -1.30         7.74E-02         1.08           RASA1         RAS p21 protein activator (GTPase activating protein) 1         1.26E-03         -1.18         6.88E-04         -1.19         8.24E-01         1.01           RGS4         regulator of G-protein signaling 4         8.7	NOMO2 ///	modulator 5						
PAK1       p21 protein (Cdc42/Rac)-activated kinase 1       4.56E-04       -1.22       9.67E-03       -1.15       2.53E-01       -1.06         PLD3       phospholipase D family, member 3       1.21E-03       -1.15       2.60E-03       -1.14       7.76E-01       -1.01         PLD1       proteolipid protein 1       1.25E-02       -1.12       1.06E-02       -1.12       9.47E-01       1.00         PRKACB       protein kinase, cAMP-dependent, catalytic, beta       4.72E-08       -1.36       7.16E-08       -1.35       8.92E-01       -1.01         PRKACG       protein kinase, C, gamma       2.15E-03       -1.21       1.318E-07       -1.26       8.14E-02       1.08         PTPRS       protein nyrosine phosphatase, receptor type, S       2.50E-03       -1.21       3.18E-07       -1.30       7.74E-02       1.08         RAB3A       RAB4A, member RAS oncogene family       3.21E-06       -1.27       6.88E-04       -1.18       7.55E-02       -1.08         RASA1       RAS p21 protein asignaling 4       8.76E-07       -1.31       1.51E-07       -1.34       5.67E-01       1.01         RGS4       regulator of G-protein signaling 4       8.76E-07       -1.31       6.21E-04       -1.33       5.67E-01       1.01	NRCAM	neuronal cell adhesion molecule	1.05E-06	-1.34	3.20E-05	-1.27	2.65E-01	-1.06
PLD3       phospholipase D family, member 3       1.21E-03       -1.15       2.60E-03       -1.14       7.76E-01       -1.01         PLD1       proteolipid protein 1       1.25E-02       -1.12       1.06E-02       -1.12       9.47E-01       1.00         PRKACB       protein kinase, c, AMP-dependent, catalytic, beta       4.72E-08       -1.36       8.14E-02       1.00         PRKCG       protein kinase, C, amma       2.15E-03       -1.17       1.28E-05       -1.26       8.14E-02       1.08         PTPRS       protein kinase, C, amma       2.15E-03       -1.23       6.67E-04       -1.26       6.28E-01       1.03         RAB6A       RAB6A, member RAS oncogene family       3.21E-06       -1.27       6.88E-04       -1.18       7.57E-02       -1.08         RASA1       RAS p21 protein activator (GTPase activating protein) 1       1.26E-03       -1.18       6.84E-04       -1.19       8.24E-01       1.01         RGS4       regulator of G-protein signaling 4       8.76E-07       -1.31       1.51E-07       -1.34       5.67E-01       1.03         RHOB       ras homolog gene family, member B       1.02E-06       -1.26       6.86E-07       -1.37       8.99E-01       1.01         RCJA2       solute carrier family 3 (ac	PAK1	p21 protein (Cdc42/Rac)-activated kinase 1	4.56E-04	-1.22	9.67E-03	-1.15	2.53E-01	-1.06
PLP1       proteolipid protein       1.25E-02       -1.12       1.06E-02       -1.12       9.47E-01       1.00         PRKACB       protein kinase, CAMP-dependent, catalytic, beta       4.72E-08       -1.36       7.16E-08       -1.35       8.92E-01       -1.01         PRKCG       protein kinase, C, gamma       2.15E-03       -1.17       1.28E-05       -1.26       8.14E-02       1.03         RAB3A       RAB3A, member RAS oncogene family       7.58E-05       -1.21       3.18E-07       -1.30       7.74E-02       1.08         RASA1       RAS pal protein atviors (GTPase activating protein) 1       1.26E-03       -1.18       6.84E-04       -1.19       8.24E-01       1.01         RGS4       regulator of G-protein signaling 4       8.76E-07       -1.31       1.51E-07       -1.34       5.67E-01       1.03         RHOB       ras homolog gene family, member B       1.02E-06       -1.36       6.86E-07       -1.37       8.99E-01       1.01         RGS4       regulator of G-protein signaling 4       8.76E-07       -1.21       3.09E-02       -1.24       7.75E-01       1.02         ROB       RAR-related orphan receptor B       2.58E-04       -1.26       2.64E-06       -1.36       1.63E-01       1.08         SFR	PLD3	phospholipase D family, member 3	1.21E-03	-1.15	2.60E-03	-1.14	7.76E-01	-1.01
PRKACB       protein kinase, cAMP-dependent, catalytic, beta       4.72E-08       -1.36       7.16E-08       -1.35       8.92E-01       -1.01         PRKCG       protein kinase, c, gamma       2.15E-03       -1.17       1.28E-05       -1.26       8.14E-02       1.08         PTPRS       protein tyrosine phosphatase, receptor type, S       2.50E-03       -1.23       6.67E-04       -1.26       6.28E-01       1.03         RAB3A       RAB3A, member RAS oncogene family       7.58E-05       -1.21       3.18E-07       -1.30       7.74E-02       1.08         RAB6A       RAB6A, member RAS oncogene family       3.21E-06       -1.27       6.88E-04       -1.18       7.55E-02       -1.08         RAS4       regulator of G-protein signaling 4       8.76E-07       -1.31       1.51E-07       -1.34       5.67E-01       1.03         ROB       ras homolog gene family, member B       1.02E-06       -1.36       6.88E-04       -1.23       7.57E-01       -1.02         RUNX1T1       run-related orphan receptor B       2.58E-04       -1.25       6.22E-04       -1.34       8.31E-01       1.01         SLC3A2       solute carrier family 3 (activators of dibasic and neutral amino acid       6.39E-03       -1.12       3.09E-02       -1.10       5.05E-01	PLP1	proteolipid protein 1	1.25E-02	-1.12	1.06E-02	-1.12	9.47E-01	1.00
PRKCG       protein kinase C, gamma       2.15E-03       -1.17       1.28E-05       -1.26       8.14E-02       1.08         PTPRS       protein tyrosine phosphatase, receptor type, S       2.50E-03       -1.23       6.67E-04       -1.26       6.28E-01       1.03         RAB3A       RAB3A, member RAS oncogene family       7.58E-05       -1.21       3.18E-07       -1.30       7.74E-02       1.08         RAB6A       RAB6A, member RAS oncogene family       3.21E-06       -1.27       6.88E-04       -1.18       7.55E-02       -1.08         RASA1       RAS p21 protein activator (GTPase activating protein) 1       1.26E-03       -1.18       6.84E-04       -1.19       8.24E-01       1.01         RGS4       regulator of G-protein signaling 4       8.76E-07       -1.31       1.51E-07       -1.34       5.67E-01       1.03         RHOB       ras homolog gene family, member B       1.002E-06       -1.26       6.48E-04       -1.23       7.57E-01       -1.02         RUNX1T1       runt-related transcription factor 1; translocated to, 1 (cyclin D-related)       1.83E-04       -1.25       6.24E-06       -1.36       6.48E-07       -1.34       8.31E-01       1.01         SIC3A2       splicing factor, arginine/serine-rich 3       1.25E-06       -1.22	PRKACB	protein kinase, cAMP-dependent, catalytic, beta	4.72E-08	-1.36	7.16E-08	-1.35	8.92E-01	-1.01
PTPRS       protein tyrosine phosphatase, receptor type, S       2.50E-03       -1.23       6.67E-04       -1.26       6.28E-01       1.03         RAB3A       RAB3A, member RAS oncogene family       7.58E-05       -1.21       3.18E-07       -1.30       7.74E-02       1.08         RAB6A       RAB6A, member RAS oncogene family       3.21E-06       -1.27       6.88E-04       -1.18       7.55E-02       -1.08         RASA1       RAS 21 protein activator (GTPase activating protein) 1       1.26E-03       -1.18       6.84E-04       -1.19       8.24E-01       1.01         RGS4       regulator of G-protein signaling 4       8.76E-07       -1.31       1.51E-07       -1.34       5.67E-01       1.03         RHOB       ras homolog gene family, member B       1.002E-06       -1.36       6.86E-07       -1.37       8.99E-01       1.01         RORB       RAR-related orphan receptor B       2.58E-04       -1.25       6.22E-04       -1.23       7.57E-01       -1.02         RUNXIT1       runt-related transcription factor 1; translocated to, 1 (cyclin D-related)       1.83E-04       -1.12       3.09E-02       -1.10       5.05E-01       -1.03         SRA23       synaptosomal-associated protein, 25 kDa       4.23E-02       -1.12       3.09E-02       -1.10	PRKCG	protein kinase C, gamma	2.15E-03	-1.17	1.28E-05	-1.26	8.14E-02	1.08
RAB3A       RAB3A, member RAS oncogene family       7.58E-05       -1.21       3.18E-07       -1.30       7.74E-02       1.08         RAB6A       RAB6A, member RAS oncogene family       3.21E-06       -1.27       6.88E-04       -1.18       7.55E-02       -1.08         RASA1       RAS p21 protein activator (GTPase activating protein) 1       1.26E-03       -1.18       6.84E-04       -1.19       8.24E-01       1.01         RGS4       regulator of G-protein signaling 4       8.76E-07       -1.31       1.51E-07       -1.37       8.99E-01       1.01         ROB       ras homolog gene family, member B       1.02E-06       -1.26       6.48E-07       -1.37       8.99E-01       1.01         RORB       RAR-related orphan receptor B       2.58E-04       -1.26       2.64E-06       -1.36       1.63E-01       1.08         SFRS3       splicing factor, arginine/serine-rich 3       1.25E-06       -1.32       6.48E-07       -1.34       8.31E-01       1.01         SLC3A2       solute carrier family 3 (activators of dibasic and neutral amino acid       6.39E-03       -1.12       3.09E-02       -1.10       5.05E-01       -1.03         SYN1       synapsin I       5.38E-04       -1.17       4.61E-07       -1.29       2.26E-02       1.10	PTPRS	protein tyrosine phosphatase, receptor type, S	2.50E-03	-1.23	6.67E-04	-1.26	6.28E-01	1.03
RAB6A       RAB6A, member RAS oncogene family       3.21E-06       -1.27       6.88E-04       -1.18       7.55E-02       -1.08         RASA1       RAS p21 protein activator (GTPase activating protein) 1       1.26E-03       -1.18       6.84E-04       -1.19       8.24E-01       1.01         RGS4       regulator of G-protein signaling 4       8.76E-07       -1.31       1.51E-07       -1.34       5.67E-01       1.03         RHOB       ras homolog gene family, member B       1.02E-06       -1.25       6.22E-04       -1.23       7.57E-01       1.01         RORB       RAR-related orphan receptor B       2.58E-04       -1.26       2.64E-06       -1.36       1.63E-01       1.08         SFRS3       splicing factor, arginine/serine-rich 3       1.25E-06       -1.32       6.48E-07       -1.34       8.31E-01       1.01         SLC3A2       solute carrier family 3 (activators of dibasic and neutral amino acid       6.39E-03       -1.12       3.09E-02       -1.10       5.05E-01       -1.03         SYN1       synapsin I       5.38E-04       -1.17       4.61E-07       -1.29       2.26E-02       1.10         THRA       thyroid hormone receptor, alpha (erythroblastic leukemia viral       2.38E-02       -1.11       2.77E-02       -1.11       9.45E-	RAB3A	RAB3A, member RAS oncogene family	7.58E-05	-1.21	3.18E-07	-1.30	7.74E-02	1.08
RASA1       RAS p21 protein activator (GTPase activating protein) 1       1.26E-03       -1.18       6.84E-04       -1.19       8.24E-01       1.01         RGS4       regulator of G-protein signaling 4       8.76E-07       -1.31       1.51E-07       -1.34       5.67E-01       1.03         RHOB       ras homolog gene family, member B       1.02E-06       -1.36       6.86E-07       -1.37       8.99E-01       1.01         RORB       RAR-related orphan receptor B       2.58E-04       -1.25       6.22E-04       -1.23       7.57E-01       -1.02         RUNX1T1       runt-related transcription factor 1; translocated to, 1 (cyclin D-related)       1.83E-04       -1.26       2.64E-06       -1.34       8.31E-01       1.01         SFR53       splicing factor, arginine/serine-rich 3       1.25E-06       -1.12       3.09E-02       -1.10       5.05E-01       -1.03         transport)       SNAP25       synaptosomal-associated protein, 25 kDa       4.23E-02       -1.14       2.42E-02       -1.15       7.97E-01       1.02         SYN1       synaptosomal-associated protein 2-like       9.94E-04       -1.22       3.54E-04       -1.25       7.13E-01       -1.00         (v-erb-a) oncogen       UBAP2L       ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)       <	RAB6A	RAB6A, member RAS oncogene family	3.21E-06	-1.27	6.88E-04	-1.18	7.55E-02	-1.08
RGS4       regulator of G-protein signaling 4       8.76E-07       -1.31       1.51E-07       -1.34       5.67E-01       1.03         RHOB       ras homolog gene family, member B       1.02E-06       -1.36       6.86E-07       -1.37       8.99E-01       1.01         RORB       RAR-related orphan receptor B       2.58E-04       -1.25       6.22E-04       -1.23       7.57E-01       -1.02         RUNX1T1       runt-related transcription factor 1; translocated to, 1 (cyclin D-related)       1.83E-04       -1.26       2.64E-06       -1.34       8.31E-01       1.01         SFRS3       splicing factor, arginine/serine-rich 3       1.25E-06       -1.32       6.48E-07       -1.34       8.31E-01       1.01         SLC3A2       solute carrier family 3 (activators of dibasic and neutral amino acid transport)       5.05E-01       -1.03       5.05E-01       -1.03         SNAP25       synaptosomal-associated protein, 25 kDa       4.23E-02       -1.14       2.42E-02       -1.15       7.97E-01       1.02         SYN1       synapsin I       5.38E-04       -1.17       4.61E-07       -1.29       2.26E-02       1.10         THRA       thyroid hormone receptor, alpha (erythroblastic leukemia viral (v-erb-a) oncogen       2.38E-04       -1.21       2.45E-04       -1.25	RASA1	RAS p21 protein activator (GTPase activating protein) 1	1.26E-03	-1.18	6.84E-04	-1.19	8.24E-01	1.01
RHOB       ras homolog gene family, member B       1.02E-06       -1.36       6.86E-07       -1.37       8.99E-01       1.01         RORB       RAR-related orphan receptor B       2.58E-04       -1.25       6.22E-04       -1.23       7.57E-01       -1.02         RUNX1T1       runt-related transcription factor 1; translocated to, 1 (cyclin D-related)       1.83E-04       -1.26       2.64E-06       -1.36       1.63E-01       1.08         SFRS3       splicing factor, arginine/serine-rich 3       1.25E-06       -1.32       6.48E-07       -1.34       8.31E-01       1.01         SLC3A2       solute carrier family 3 (activators of dibasic and neutral amino acid transport)       6.39E-03       -1.12       3.09E-02       -1.15       7.97E-01       1.02         SNAP25       synaptosomal-associated protein, 25 kDa       4.23E-02       -1.14       2.42E-02       -1.15       7.97E-01       1.02         SYN1       synapsin I       5.38E-04       -1.17       4.61E-07       -1.29       2.26E-02       1.10         THRA       thyroid hormone receptor, alpha (erythroblastic leukemia viral (v-erb-a) oncogen       2.38E-04       -1.21       2.45E-04       -1.25       7.13E-01       -1.00         UBAP2L       ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)       2.40E-04	RGS4	regulator of G-protein signaling 4	8.76E-07	-1.31	1.51E-07	-1.34	5.67E-01	1.03
RORB       RAR-related orphan receptor B       2.58E-04       -1.25       6.22E-04       -1.23       7.57E-01       -1.02         RUNX1T1       runt-related transcription factor 1; translocated to, 1 (cyclin D-related)       1.83E-04       -1.26       2.64E-06       -1.36       1.63E-01       1.08         SFRS3       splicing factor, arginine/serine-rich 3       1.25E-06       -1.32       6.48E-07       -1.34       8.31E-01       1.01         SLC3A2       solute carrier family 3 (activators of dibasic and neutral amino acid transport)       6.39E-03       -1.12       3.09E-02       -1.10       5.05E-01       -1.03         SNAP25       synaptosomal-associated protein, 25 kDa       4.23E-02       -1.14       2.42E-02       -1.15       7.97E-01       1.02         SYN1       synapsin I       5.38E-04       -1.17       4.61E-07       -1.29       2.26E-02       1.10         THRA       thyroid hormone receptor, alpha (erythroblastic leukemia viral (v-erb-a) oncogen       0.38E-04       -1.21       2.47E-04       -1.25       7.13E-01       1.02         UBAP2L       ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)       2.40E-04       -1.21       2.45E-04       -1.21       9.94E-01       -1.00         UBE2S       ubiquitin-conjugating enzyme E2S       8.75E-03 <td>RHOB</td> <td>ras homolog gene family, member B</td> <td>1.02E-06</td> <td>-1.36</td> <td>6.86E-07</td> <td>-1.37</td> <td>8.99E-01</td> <td>1.01</td>	RHOB	ras homolog gene family, member B	1.02E-06	-1.36	6.86E-07	-1.37	8.99E-01	1.01
RUNX1T1       runt-related transcription factor 1; translocated to, 1 (cyclin D-related)       1.83E-04       -1.26       2.64E-06       -1.36       1.63E-01       1.08         SFRS3       splicing factor, arginine/serine-rich 3       1.25E-06       -1.32       6.48E-07       -1.34       8.31E-01       1.01         SLC3A2       solute carrier family 3 (activators of dibasic and neutral amino acid transport)       6.39E-03       -1.12       3.09E-02       -1.10       5.05E-01       -1.03         SNAP25       synaptosomal-associated protein, 25 kDa       4.23E-02       -1.14       2.42E-02       -1.15       7.97E-01       1.02         SYN1       synapsin I       5.38E-04       -1.17       4.61E-07       -1.29       2.26E-02       1.10         THRA       thyroid hormone receptor, alpha (erythroblastic leukemia viral (v-erb-a) oncogen       2.38E-02       -1.11       2.77E-02       -1.11       9.45E-01       -1.00         UBAP2L       ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)       2.40E-04       -1.21       2.45E-04       -1.21       9.94E-01       -1.00         UBE2S       ubiquitin-conjugating enzyme E2S       8.75E-03       -1.14       4.48E-02       -1.10       4.76E-01       -1.03         VDAC1       voltage-dependent anion channel 1       4.28E-	RORB	RAR-related orphan receptor B	2.58E-04	-1.25	6.22E-04	-1.23	7.57E-01	-1.02
SFRS3       splicing factor, arginine/serine-rich 3       1.25E-06       -1.32       6.48E-07       -1.34       8.31E-01       1.01         SLC3A2       solute carrier family 3 (activators of dibasic and neutral amino acid transport)       6.39E-03       -1.12       3.09E-02       -1.10       5.05E-01       -1.03         SNAP25       synaptosomal-associated protein, 25 kDa       4.23E-02       -1.14       2.42E-02       -1.15       7.97E-01       1.02         SYN1       synapsin I       5.38E-04       -1.17       4.61E-07       -1.29       2.26E-02       1.10         THRA       thyroid hormone receptor, alpha (erythroblastic leukemia viral (v-erb-a) oncogen       2.38E-02       -1.11       2.77E-02       -1.11       9.45E-01       -1.00         UBAP2L       ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)       2.40E-04       -1.21       2.45E-04       -1.21       9.94E-01       -1.00         UBE2S       ubiquitin-conjugating enzyme E2S       8.75E-03       -1.14       4.48E-02       -1.10       4.76E-01       -1.03         VDAC1       voltage-dependent anion channel 1       4.28E-02       -1.11       3.18E-02       -1.12       8.91E-01       1.01         YWHAZ       tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta pol       7.	RUNX1T1	runt-related transcription factor 1; translocated to, 1 (cyclin D-related)	1.83E-04	-1.26	2.64E-06	-1.36	1.63E-01	1.08
SLC3A2       solute carrier family 3 (activators of dibasic and neutral amino acid transport)       6.39E-03       -1.12       3.09E-02       -1.10       5.05E-01       -1.03         SNAP25       synaptosomal-associated protein, 25 kDa       4.23E-02       -1.14       2.42E-02       -1.15       7.97E-01       1.02         SYN1       synapsin I       5.38E-04       -1.17       4.61E-07       -1.29       2.26E-02       1.10         THRA       thyroid hormone receptor, alpha (erythroblastic leukemia viral (v-erb-a) oncogen       2.38E-02       -1.11       2.77E-02       -1.11       9.45E-01       -1.00         UBAP2L       ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)       2.40E-04       -1.21       2.45E-04       -1.21       9.94E-01       -1.00         UBE2S       ubiquitin-conjugating enzyme E2S       8.75E-03       -1.14       4.48E-02       -1.10       4.76E-01       -1.03         VDAC1       voltage-dependent anion channel 1       4.28E-02       -1.11       3.18E-02       -1.12       8.91E-01       1.01         YWHAZ       tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation       7.41E-04       -1.20       1.60E-02       -1.14       2.38E-01       -1.06         ZNF238       zinc finger protein 238       4.36E-04       -1.20	SFRS3	splicing factor, arginine/serine-rich 3	1.25E-06	-1.32	6.48E-07	-1.34	8.31E-01	1.01
transport)           SNAP25         synaptosomal-associated protein, 25 kDa         4.23E-02         -1.14         2.42E-02         -1.15         7.97E-01         1.02           SYN1         synapsin I         5.38E-04         -1.17         4.61E-07         -1.29         2.26E-02         1.10           THRA         thyroid hormone receptor, alpha (erythroblastic leukemia viral (v-erb-a) oncogen         2.38E-02         -1.11         2.77E-02         -1.11         9.45E-01         -1.00           UBAP2L         ubiquitin-associated protein 2-like         9.94E-04         -1.22         3.54E-04         -1.25         7.13E-01         1.02           UBE2D3         ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)         2.40E-04         -1.21         2.45E-04         -1.21         9.94E-01         -1.00           UBE2S         ubiquitin-conjugating enzyme E2S         8.75E-03         -1.14         4.48E-02         -1.10         4.76E-01         -1.03           VDAC1         voltage-dependent anion channel 1         4.28E-02         -1.11         3.18E-02         -1.12         8.91E-01         1.01           YWHAZ         tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation         7.41E-04         -1.20         1.60E-02         -1.14         2.38E-01         -1.06     <	SLC3A2	solute carrier family 3 (activators of dibasic and neutral amino acid	6.39E-03	-1.12	3.09E-02	-1.10	5.05E-01	-1.03
SNAP25       synaptosomal-associated protein, 25 kDa       4.23E-02       -1.14       2.42E-02       -1.15       7.97E-01       1.02         SYN1       synapsin I       5.38E-04       -1.17       4.61E-07       -1.29       2.26E-02       1.10         THRA       thyroid hormone receptor, alpha (erythroblastic leukemia viral (v-erb-a) oncogen       2.38E-02       -1.11       2.77E-02       -1.11       9.45E-01       -1.00         UBAP2L       ubiquitin-associated protein 2-like       9.94E-04       -1.22       3.54E-04       -1.25       7.13E-01       1.02         UBE2D3       ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)       2.40E-04       -1.21       2.45E-04       -1.21       9.94E-01       -1.00         UBE2S       ubiquitin-conjugating enzyme E2S       8.75E-03       -1.14       4.48E-02       -1.10       4.76E-01       -1.03         VDAC1       voltage-dependent anion channel 1       4.28E-02       -1.11       3.18E-02       -1.12       8.91E-01       1.01         YWHAZ       tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation       7.41E-04       -1.20       1.60E-02       -1.14       2.38E-01       -1.06         ZNF238       zinc finger protein 238       4.36E-04       -1.20       4.49E-04       -1.20		transport)						
SYN1       synapsin I       5.38E-04       -1.17       4.61E-07       -1.29       2.26E-02       1.10         THRA       thyroid hormone receptor, alpha (erythroblastic leukemia viral (v-erb-a) oncogen       2.38E-02       -1.11       2.77E-02       -1.11       9.45E-01       -1.00         UBAP2L       ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)       2.40E-04       -1.21       2.45E-04       -1.25       7.13E-01       1.02         UBE2S       ubiquitin-conjugating enzyme E2S       8.75E-03       -1.14       4.48E-02       -1.10       4.76E-01       -1.03         VDAC1       voltage-dependent anion channel 1       4.28E-02       -1.11       3.18E-02       -1.12       8.91E-01       1.01         YWHAZ       tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation       7.41E-04       -1.20       1.60E-02       -1.14       2.38E-01       -1.06         ZNF238       zinc finger protein 238       4.36E-04       -1.20       4.49E-04       -1.20       9.92E-01       -1.00	SNAP25	synaptosomal-associated protein, 25 kDa	4.23E-02	-1.14	2.42E-02	-1.15	7.97E-01	1.02
THRA       thyroid hormone receptor, alpha (erythroblastic leukemia viral (v-erb-a) oncogen       2.38E-02       -1.11       2.77E-02       -1.11       9.45E-01       -1.00         UBAP2L       ubiquitin-associated protein 2-like       9.94E-04       -1.22       3.54E-04       -1.25       7.13E-01       1.02         UBE2D3       ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)       2.40E-04       -1.21       2.45E-04       -1.21       9.94E-01       -1.00         UBE2S       ubiquitin-conjugating enzyme E2S       8.75E-03       -1.14       4.48E-02       -1.10       4.76E-01       -1.03         VDAC1       voltage-dependent anion channel 1       4.28E-02       -1.11       3.18E-02       -1.12       8.91E-01       1.01         YWHAZ       tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation       7.41E-04       -1.20       1.60E-02       -1.14       2.38E-01       -1.06         ZNF238       zinc finger protein 238       4.36E-04       -1.20       4.49E-04       -1.20       9.92E-01       -1.00	SYN1	synapsin I	5.38E-04	-1.17	4.61E-07	-1.29	2.26E-02	1.10
(v-erb-a) oncogen           UBAP2L         ubiquitin-associated protein 2-like         9.94E-04         -1.22         3.54E-04         -1.25         7.13E-01         1.02           UBE2D3         ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)         2.40E-04         -1.21         2.45E-04         -1.21         9.94E-01         -1.00           UBE2S         ubiquitin-conjugating enzyme E2S         8.75E-03         -1.14         4.48E-02         -1.10         4.76E-01         -1.03           VDAC1         voltage-dependent anion channel 1         4.28E-02         -1.11         3.18E-02         -1.12         8.91E-01         1.01           YWHAZ         tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation         7.41E-04         -1.20         1.60E-02         -1.14         2.38E-01         -1.06	THRA	thyroid hormone receptor, alpha (erythroblastic leukemia viral	2.38E-02	-1.11	2.77E-02	-1.11	9.45E-01	-1.00
UBAP2L         ubiquitin-associated protein 2-like         9.94E-04         -1.22         3.54E-04         -1.25         7.13E-01         1.02           UBE2D3         ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)         2.40E-04         -1.21         2.45E-04         -1.21         9.94E-01         -1.00           UBE2S         ubiquitin-conjugating enzyme E2S         8.75E-03         -1.14         4.48E-02         -1.10         4.76E-01         -1.03           VDAC1         voltage-dependent anion channel 1         4.28E-02         -1.11         3.18E-02         -1.12         8.91E-01         1.01           YWHAZ         tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation         7.41E-04         -1.20         1.60E-02         -1.14         2.38E-01         -1.06		(v-erb-a) oncogen						
UBE2D3       ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)       2.40E-04       -1.21       2.45E-04       -1.21       9.94E-01       -1.00         UBE2S       ubiquitin-conjugating enzyme E2S       8.75E-03       -1.14       4.48E-02       -1.10       4.76E-01       -1.03         VDAC1       voltage-dependent anion channel 1       4.28E-02       -1.11       3.18E-02       -1.12       8.91E-01       1.01         YWHAZ       tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation       7.41E-04       -1.20       1.60E-02       -1.14       2.38E-01       -1.06	UBAP2L	ubiquitin-associated protein 2-like	9.94E-04	-1.22	3.54E-04	-1.25	7.13E-01	1.02
UBE2S         ubiquitin-conjugating enzyme E2S         8.75E-03         -1.14         4.48E-02         -1.10         4.76E-01         -1.03           VDAC1         voltage-dependent anion channel 1         4.28E-02         -1.11         3.18E-02         -1.12         8.91E-01         1.01           YWHAZ         tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta pol         7.41E-04         -1.20         1.60E-02         -1.14         2.38E-01         -1.06           ZNF238         zinc finger protein 238         4.36E-04         -1.20         4.49E-04         -1.20         9.92E-01         -1.00	UBE2D3	ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)	2.40E-04	-1.21	2.45E-04	-1.21	9.94E-01	-1.00
VDAC1         voltage-dependent anion channel 1         4.28E-02         -1.11         3.18E-02         -1.12         8.91E-01         1.01           YWHAZ         tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation         7.41E-04         -1.20         1.60E-02         -1.14         2.38E-01         -1.06           protein, zeta pol         -         -         -         -         -         -         -         -         -         -         -         -         -         -         1.00           ZNF238         zinc finger protein 238         4.36E-04         -1.20         4.49E-04         -1.20         9.92E-01         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         1.00         -         -         -         -         -         -         -         -         -         -         1.00         -         -         1.00         -         -         -         -         -         1.00         -         -         1.00         -         -         -         1.00         -         -         -         -         1.00         -	UBE2S	ubiquitin-conjugating enzyme E2S	8.75E-03	-1.14	4.48E-02	-1.10	4.76E-01	-1.03
Y WHAZ         tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation         7.41E-04         -1.20         1.60E-02         -1.14         2.38E-01         -1.06           protein, zeta pol         ZNF238         zinc finger protein 238         4.36E-04         -1.20         4.49E-04         -1.20         9.92E-01         -1.00	VDAC1	voltage-dependent anion channel 1	4.28E-02	-1.11	3.18E-02	-1.12	8.91E-01	1.01
ZNF238         zinc finger protein 238         4.36E-04         -1.20         4.49E-04         -1.20         9.92E-01         -1.00	YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta pol	7.41E-04	-1.20	1.60E-02	-1.14	2.38E-01	-1.06
	ZNF238	zinc finger protein 238	4.36E-04	-1.20	4.49E-04	-1.20	9.92E-01	-1.00

This table shows the 50 normalized genes that fulfilled three criteria on the HU6800 array. FC = Fold change.

**Table 8.** IPA was used to functionally annotate 50 PCP-dysregulated genes that were normalized by olanzapine coadministration

Category	B-H p value	Genes, n
Genetic disorder Neurological disease Skeletal and muscular disorders Cell death Cell signaling	7.13E-05 7.13E-05 7.13E-05 2.90E-04 2.07E-03	34 29 19 4 3
e e		

The top five over-represented biological functions are shown. B-H = Benjamini-Hochberg.

ed in schizophrenia and neurological disorders, further supporting the use of PCP treatment as a model system for the study of glutamate dysfunction-related gene expression alterations in schizophrenia. Genes associated with cell death were also significantly altered, which was expected given the previously demonstrated neurotoxic effects of PCP [12]. It was not surprising that genes involved in synaptic long potentiation were altered by the NMDA receptor antagonist PCP given the role of NMDA and long-term potentiation [13]. This is consistent with previous work showing overrepresentation of altered expression of synapse-related genes in a chronic rat PCP model of schizophrenia [14].

Antipsychotic treatment with OLZ reversed the effects of PCP administration for 50 genes. Again, there was an overrepresentation of OLZ + PCP genes with those previously implicated in the etiology of schizophrenia and cell death (n = 24). This is interesting in light of previous work suggesting neuroprotective effects of OLZ in rodents and humans [15–19] and raises the question of whether such changes in gene expression are related to antipsychotic efficacy.

We assessed the effects of AOLZ and OLZ as well as AHAL and HAL administration on gene expression in the absence of PCP and found very little overlap between the genes with expression altered by antipsychotic treatment compared to those normalized by OLZ + PCP, suggesting that antipsychotics have a limited effect on expression of these genes in the absence of glutamate dysfunction. There were 12 significant gene expression alterations in OLZ-administered animals versus those administered VEH (MEF2C, CTNNA2, NRGN, MIF, TYRO3, BRD8, STMN2, YWHAH, ATP1B2, PPIA, GRIA3, and DLG4), including an overrepresentation of genes implicated in glutamate receptor signaling, ERK5 signaling, and calcium signaling, suggesting possible mechanisms by which PCP effects on expression are reversed or prevented by OLZ coadministration. Interestingly, neurogranin (NRGN), which plays a role in longterm potentiation [20], has been implicated in schizophrenia in a clinical association study [21, 22] and in an immunoreactivity study in postmortem human brain tissue [23].

IPA analysis identified one gene network connecting 17 genes normalized by OLZ. One gene of interest in this gene network was regulator of G protein signaling 4 (RGS4). RGS4 is a GTPase activator protein that has been shown to interact with opiate, adrenergic, muscarinic, and glutamate receptors, and its expression can influence synaptic function [24]. It has been previously implicated in the etiology of schizophrenia (for reviews, see [25-27]), and RGS4 genotypes at markers rs2661319 and rs2842030 have previously been shown to be associated with more severe baseline PANSS total scores and to predict responsiveness to antipsychotic treatment [28]. RSG4 was not significantly altered in OLZ or HAL compared to VEH controls, consistent with previous findings that expression of this gene is not altered by antipsychotic treatment in the absence of glutamate dysfunction [27]. However, RGS4 was one of the most significantly differentially expressed genes in the comparison between PCP- and PCP + OLZ-administered animals and may be of interest for investigation as a target for antipsychotic action. Also of interest within the network were SNAP-25 and SYN1, which have been shown to be decreased in postmortem brains of subjects with schizophrenia and bipolar disorder, respectively [29, 30], and YWHAZ, which has been identified as a schizophrenia susceptibility gene [31].

DAVID Bioinformatics Database identified two transcription factors associated with the regulation of a significant number of OLZ normalized genes. These transcription factors were SOX5 and MEF2 (see online suppl. tables 5, 6), which have binding sites to possibly regulate 36 and 41 of the 50 OLZ-reversed genes, respectively. Interestingly, an SNP in the SOX5 gene has been previously associated with metabolic adverse events during treatment with antipsychotics in schizophrenia, further implicating this transcription factor in antipsychotic response.

One shortcoming of the present study was that gene expression was only investigated in one brain region. Future work will be necessary to determine whether the changes in gene expression observed in the current study were specific to the PFC or generalizable across



**Fig. 5.** A total of 146 genes were dysregulated in PCP-administered animals compared to VEH controls. Treatment with OLZ reversed 50 of these expression alterations.

**Fig. 6.** The Venn diagram shows the overlap between probe sets altered in expression by AOLZ and OLZ treatment and 50 PCP-induced expression alterations that were normalized by OLZ (fig. 5).

**Table 9.** Using a set of 50 PCP-dysregulated genes that were normalized by olanzapine coadministration, IPA canonical pathway analysis identified the following over-represented canonical pathways after correcting for multiple comparisons

Ingenuity canonical pathways	B-H p value	Genes
Melatonin signaling	9.12E-03	PRKACB, RORB, PRKCG, CAMK2G
Calcium signaling	9.33E-03	PRKACB, MEF2C, ATP2A2, ATP2B2, CAMK2G
FYN receptor-mediated phagocytosis in	9.33E-03	PAK1, PLD3, ACTB, PRKCG
macrophages and monocytes		
G protein-coupled receptor signaling	1.35E-02	PRKACB, RGS4, RASA1, PRKCG, CAMK2G
Molecular mechanisms of cancer	1.35E-02	PRKACB, PAK1, RHOB, RASA1, PRKCG, CAMK2G

B-H = Benjamini-Hochberg.

regions. A second shortcoming of this study was that findings were not validated by qPCR or at the protein level. However, the use of two different gene expression platforms and the use of technical duplicates within each platform to find replicable genes strongly support the reliability of the present findings. These follow-up studies were not conducted as tissue from the primates is not available.

It was unclear whether OLZ treatment reversed or prevented gene expression changes induced by PCP. Because animals were treated with PCP alone for 2 weeks prior to 4 weeks of OLZ coadministration, we speculate that PCPinduced changes in gene expression were reversed rather than prevented. However, because the comparison PCP group was administered PCP for 6 weeks, it is not possible to determine which PCP effects that we observed would have occurred by 2 weeks. OLZ treatment alone resulted

OLZ Reversed Brain Gene Expression Changes Induced by PCP in an upregulation of transcription factor MEF2C, which again may have mediated the upregulated expression we observed after OLZ treatment. However, the majority of OLZ changes occurred only in the presence of dysregulation, such as in the PCP model. All but one probe set that was significantly differentially expressed between PCPand VEH-administered animals was downregulated, which is inconsistent with previous microarray findings in rats which found approximately equal numbers of upand downregulated genes in response to PCP administration [32]. There were six transcription factors downregulated on both arrays: GTF2I, TCEA1, RUNX1T1, ATF6B, E2F4, and MEF2C. MEF2C is a candidate gene for schizophrenia and known to regulate neurogenesis and the excitatory synapse number. This gene is located at 5q14.3, within one of the 108 schizophrenia-associated genetic loci identified by the Psychiatric Genomics Consortium

[33]. It is possible that the downregulation of these transcription factors leads to a cascade of downregulation of gene expression in the PFC. In line with this is the observation of NMDA receptor subunit downregulation in the PFC of postmortem subjects with schizophrenia [34]. The current expression data give an understanding of drug effects of OLZ, PCP, and HAL that are otherwise difficult to obtain in the human brain and often reflect the mode of death and environmental consequences of illness. The present gene expression results are not contaminated by agonal factors and have intrinsic value for interpreting other published gene expression datasets on the human brain, since the current results are based on careful quality control of quadruplicate arrays for each sample.

Conclusions

This study is the first to examine genome-wide changes in brain gene expression influenced by PCP and the reversal of effects by antipsychotic treatment in primates. This study identified 146 genes altered in expression by PCP and found an overrepresentation of PCP- induced effects of genes implicated in cell death, neurological disorders, and schizophrenia. Canonical pathway analysis of PCP-altered genes revealed a significant overrepresentation of genes implicated in calcium signaling and synaptic long-term potentiation. Although there is no complete model of schizophrenia, which is a uniquely human disorder, the results of the present study support the use of PCP administration as a pharmacological model of glutamatergic dysfunction in schizophrenia, and we found that 34% of all genes downregulated by PCP administration are normalized by administration of OLZ. Furthermore, novel candidate genes and networks for future pharmacogenetic studies were identified.

#### **Statement of Ethics**

None.

#### **Disclosure Statement**

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