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### Title

Transcriptomic Analysis of Molecular Mechanisms of Neuroprotection by Neuregulin-1 Following Ischemic Stroke

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TRANSCRIPTOMIC ANALYSIS OF MOLECULAR MECHANISMS OF  
NEUROPROTECTION BY NERUEGULIN-1 FOLLOWING ISCHEMIC STROKE

By

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A capstone project submitted for graduation with University Honors

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## ABSTRACT

Ischemic stroke is a global health problem that is characterized by early neuronal death, apoptosis, inflammation, and oxidative stress following an obstruction of the blood supply to the brain. Previous studies have shown that ischemic stroke causes a release of pro-inflammatory cytokines that produce changes in gene expression, primarily in inflammation and cell death. Neuregulin-1 (NRG-1) is growth factor that has been investigated for its neuroprotective properties and ability to delay neuronal death following ischemic stroke. While NRG-1 has shown significant promise in preventing brain damage and stimulating post-injury repair following stroke, the mechanisms behind its neuroprotective effects are unclear. The goal of this research was to investigate the effects of NRG-1 treatment on ischemia-induced gene expression profiles following a permanent middle cerebral artery occlusion (pMCAO) in rat models. Rats were sacrificed twelve hours following vehicle or NRG-1 treatment. From the total RNA extracted from the rat brains, mRNA from the peri-infarct cortex was used to generate microarrays, which were then hybridized to an Affymetrix Rat Genome 2.0st Gene Chip and analyzed using the Affymetrix Transcriptome Analysis Console (TAC) Software. Our results show that NRG-1 delivery increases the regulation of pro-survival genes. Most notably, NRG-1 treatment upregulates the CREB1 and FOXO1 transcription factors, which are involved in increasing anti-inflammatory and cell proliferation responses and decreasing apoptosis and oxidative stress responses, respectively. These findings provide novel insight into the molecular mechanisms involved in neuregulin-1 neuroprotection. Further region-specific research is necessary to elucidate the importance of these genes in stroke and the significance of their regulation by NRG-1.

## ACKNOWLEDGEMENTS

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## INTRODUCTION

Stroke is the 5<sup>th</sup> leading cause of death worldwide, with about 87% of cases being ischemic stroke (1). Differing from hemorrhagic stroke, which occurs due to internal blood loss, ischemic stroke occurs when the brain blood supply is obstructed. Ischemic stroke is characterized by cell death, inflammation, and oxidative stress, that occur through molecular cascades and changes in regulatory gene expression (2,3). The only approved treatment for ischemic stroke is tPA, a limited and time-sensitive treatment aimed at restoring blood flow that only 3-5% of patients qualify for (4). Given the wide-spread and dire need for an effective ischemic stroke treatment that can be administered outside the three-hour therapeutic window of tPA, a better understanding of the pathophysiology associated with ischemic stroke is necessary to develop effective therapeutic treatments aimed at reducing the progression of the associated cell death.

Previous studies have shown that ischemic stroke causes a release of pro-inflammatory cytokines that produce changes in gene expression, primarily in inflammation and cell death (5,6). The initial area of injury, known as the infarct core, develops within minutes of stroke onset and develops up to three hours after stroke. The infarct core is characterized by low cerebral blood flow, oxidative stress, and excitotoxicity, which is accompanied by an increased production of inflammatory molecules. The resulting inflammation begins to affect a larger area of brain tissue, known as the ischemic penumbra, where neurons can survive up to twenty-four hours after stroke onset, prolonging the therapeutic window for ischemic stroke treatment (7–9).

Neuregulin-1 has been investigated as a potential therapeutic for ischemic stroke for its various roles in the nervous system. Neuregulin-1 is a small protein first discovered by several laboratories researching cancer biology mechanisms, cancer biology mechanisms, neuromuscular

junction function and Schwann cell proliferation. Multiple reports from our laboratory have demonstrated that the exogenous delivery of NRG-1 reduces neuronal damage in the penumbral region of rats that underwent middle cerebral artery occlusion in an extended therapeutic window (10–13). While NRG-1 has shown significant promise in preventing brain damage and stimulating post-injury repair following stroke, the regulatory mechanisms behind its neuroprotective effects are unclear. The investigation of ischemia-induced gene expression profiles following NRG-1 administration will provide valuable insight into the transcriptional regulation of these processes.

In this study, we performed a computational transcriptomic analysis to identify gene expression profiles and their associated transcriptional mechanisms affected by NRG-1 treatment twelve hours following permanent MCAO using the Transcriptome Analysis Console (TAC) software. TAC software allows for the statistical analysis of differential gene expression. To investigate mechanisms involved in the inflammatory and cell death responses that occur in the penumbra, we identified genes that were significantly regulated following NRG-1 treatment at twelve hours following ischemic stroke and the transcription factors that regulated the expression of these genes. Additionally, we verified transcriptional regulation activity of these factors through a Multiplex Transcription Factor Array. Cellular processes were investigated through literature search and STRING database analysis, and the brain cell types involved in these processes were visually displayed using immunohistochemistry (which remains incomplete due to COVID-19). Understanding the mechanisms regulated by the NRG-1 phosphorylation cascade may explain the neuroprotective effects of NRG-1 on a molecular level. These findings could support the development of clinical studies using NRG-1 to treat patients with ischemic stroke.

## METHODS

### *Animals*

All animals were treated humanely with regard for the alleviation of pain and suffering. All surgical protocols involving animals were performed by aseptic techniques and were approved by the Institutional Animal Care and Use Committee at Morehouse School of Medicine prior to the experiment. Male adult Sprague-Dawley *rattus norvegicus* (250-300g; Charles River Laboratory International, Inc., USA) were housed in standard cages in a temperature-controlled room at  $22 \pm 2^\circ\text{C}$  on a twelve-hour reverse light-dark cycle, where food and water were provided *ad libitum*.

Rats were randomly allocated into three groups: Sham (control), MCAO + vehicle treatment (MCAO), and MCAO + NRG-1 treatment (MCAO+NRG1). All rats were anesthetized with 5% isoflurane with a  $\text{O}_2/\text{N}_2\text{O}$  mixture at 30%/70%. Once anesthetized, a rectal probe monitored the core body temperature of the animals, and a Homoeothermic Blanket Control Unit was used to maintain a stable body temperature of  $37^\circ\text{C}$ . Cerebral blood flow was monitored during surgery by a continuous laser Doppler flowmeter. The Doppler probe was placed 7 mm lateral and 2 mm posterior to the bregma in a thinned cranial skull window.

Rats in the treatment groups (MCAO and MCAO+NRG1) underwent a left permanent MCAO. MCAO was induced by the intraluminal suture method previously described (12). These rats were then administered 50  $\mu\text{l}$  of NRG-1 $\beta$  (1% BSA in PBS) or 50  $\mu\text{l}$  of vehicle (1% BSA in PBS) treatment via bolus injection into the ICA through the ECA immediately before MCAO, as previously described (12). The MCAO procedure involves inserting a 4 cm length 4-0 surgical monofilament nylon suture coated with silicon from the external carotid artery (ECA) into the



internal carotid artery (ICA) and then into the Circle of Willis to permanently occlude the left middle cerebral artery (MCA). Animals in the treatment groups were sacrificed twelve hours after MCAO. Rats in the control group (Sham) underwent a similar procedure as those in the treatment groups (MCAO and MCAO+NRG1), except a 4-0 surgical monofilament was not inserted into the ICA. Rats in the control group were sacrificed three hours after the Sham procedure. All NRG-1 and vehicle treatment studies were performed in a blinded manner.

### *Microarray Analysis*

Treated animals were sacrificed twelve hours following MCAO (n = 4 for MCAO and n = 5 for MCAO+NRG1) and control animals were sacrificed three hours after sham surgery (n = 4). Brains were extracted and sectioned into 2 mm coronal sections, approximately +3.0 to -5.0 from bregma, where left cortical tissue was isolated. Left hemi-cortical tissue from Sham was used as the control group. Total RNA was extracted with TRIzol Reagent, then controlled and quantified by the Agilent 2100 Bioanalyzer. Microarrays were completed according to Applied Biosystems manufacturing guidelines, with mRNA hybridized to an Affymetrix Rat Genome 2.0st Gene Chip. Microarray chips were then used for gene expression analysis.

Statistical analysis of microarray data was completed using the Applied Biosystems Transcriptome Analysis Console (TAC) Software Package. CEL files generated from the Applied Biosystems Rat Genome 2.0 Gene Chip were imported to TAC for quality control, data normalization, and to identify differentially expressed genes. The Transcriptome Analysis approach was utilized due to its ability to simultaneously analyze a large amount of gene changes

and identify possible regulating gene groups. For differential expression analyses, a cutoff of 1.5-fold change and p-value of  $< 0.05$  were used.

TAC utilizes Principal Component Analysis (PCA) to identify patterns in experimental samples and WikiPathways to identify gene ontology and top biological processes. Lists of differentially expressed genes between different conditions were saved as a .txt file for further use in other software. Along with the WikiPathways Analysis coupled into the TAC software, other databases, such as STRING, were used to identify possible protein-protein interactions. STRING was used to identify potential “hub” genes that may regulate pathways associated with a gene set.

#### *Multiplex Transcription Factor Assay*

Brain tissues from the ipsilateral cortex, which are lateral to sections obtained for RNA extractions, was used for transcription factor assay studies ( $n = 3$  for each condition). Nuclear proteins were isolated using the Affymetrix USB Nuclear Extraction Kit and the Affymetrix Procarta Transcription Factor Assay was used to measure transcription factor DNA binding activity. All protocols were performed according to the manufacturer’s guidelines.

The Procarta detection probes and nuclear extracts from the samples were incubated for thirty minutes at  $15^{\circ}\text{C}$  to form a protein-DNA complex. Samples were washed with a cold binding buffer, incubated on ice for five minutes, centrifuged for five minutes at  $4^{\circ}\text{C}$ , and the flow through was discarded. The Protein-DNA complex was denatured at  $95^{\circ}\text{C}$  for five minutes, and then incubated with capture beads for 30 minutes at  $50^{\circ}\text{C}$  on a shaker for 400 rpm. Streptavidin-PE was added to the capture beads for thirty minutes at room temperature on a shaker for 400 rpm before being washed and resuspended in reading buffer on a shaker at 400 rpm. Results were read on the Luminex instrument (Bio-plex system 200, Bio-Rad, Hercules, California).

*Immunohistochemistry (Incomplete due to COVID-19)*

Hydroxyethyl cellulose hydrogels infused with NRG-1 were placed on adult rats following craniectomy for 3 h. Male adult Wistar rats were deeply anesthetized 3 h post hydrogel application with 2-3% isoflurane and given an IP injection of pentobarbital prior to trans-cardial perfusion with PBS, followed by cold 4% paraformaldehyde (PFA) solution in PBS for 30 min. Brains were quickly removed and incubated in formalin for 24 h. Afterwards they were cryoprotected in 30% sucrose for 48 h. The brains were then frozen in OCT compound and stored at -80°C until sectioning. Coronal sections of 10 µm thickness were cryosectioned from the entire brain of each animal. Sections were mounted on slides which were stored at -80°C until further processed.

For immunostaining, after rinsing in TBS, sections were blocked with TBS containing 10% normal donkey serum and 0.1% triton X-100 for 3 h at room temperature. Sections were incubated overnight at 4°C with TBS. Sections were washed with TBS and incubated with Streptavidin, Alexa Fluor™ 594 Conjugate (1:1000) for 1 h at room temperature. Cryosectioned brain tissues were fixed for double fluorescent immunohistochemistry to stain phosphorylated ErbB4 receptor (using pErbB4) against neurons (using NeuN), astrocytes (using GFAP), and microglia (using CD11b and Iba-1) to determine if colocalization is present.

Stained slides were imaged with a Zeiss LSM 900 confocal microscope. Images were captured at 20 high-resolution (1550 x 1550-pixel format) using a 10x objective. Each z-stack (20 µm) was merged into a single image, converted to an 8-bit TIFF file, and analyzed using Image J. Fluoresced cells were counted to quantify colocalization.

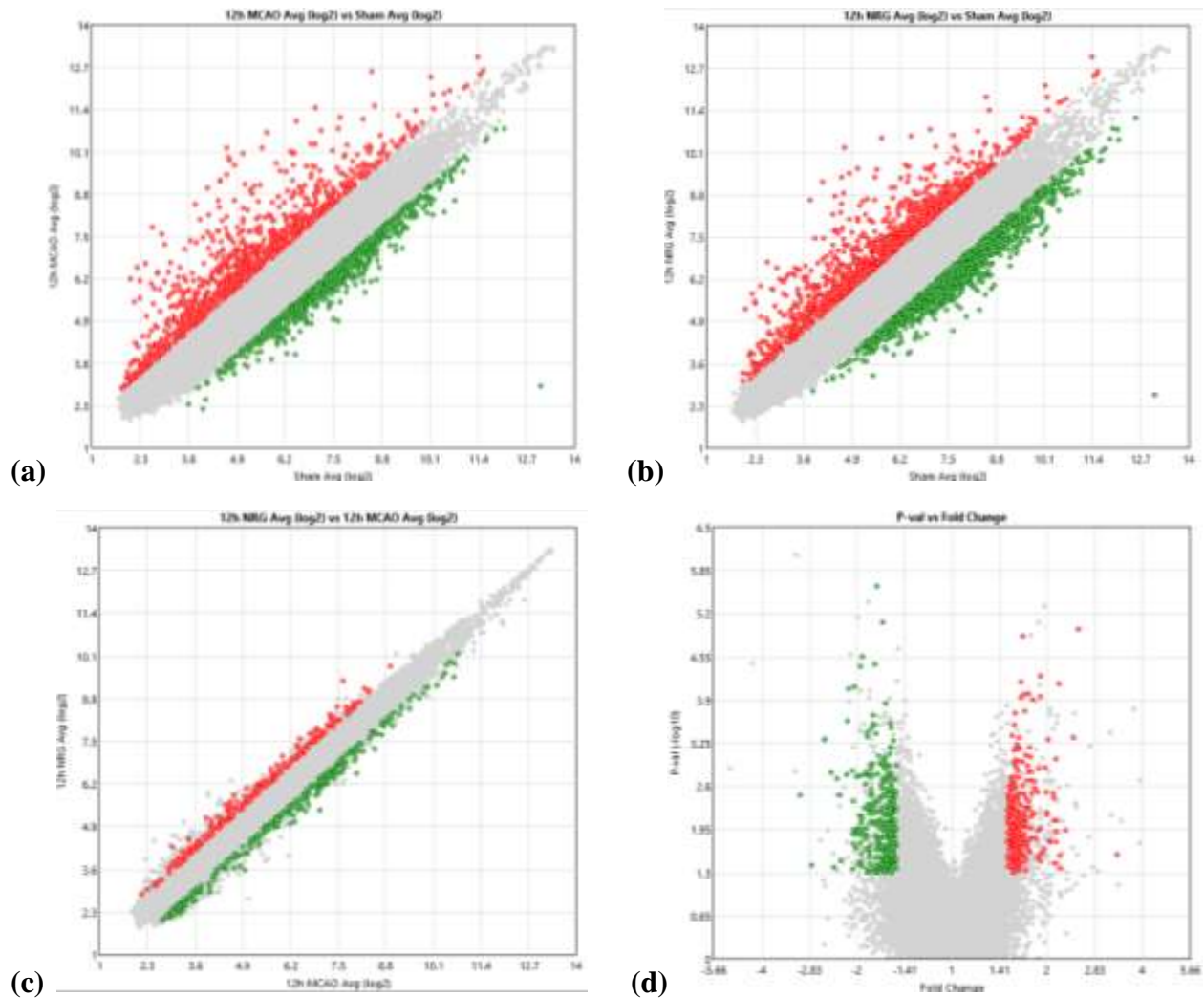
## RESULTS

### *Microarray Analysis*

Neuregulin-1 has been previously demonstrated by our lab to be neuroprotective following ischemia in rat models (12,14,15). To examine how NRG-1 alters gene expression in the ischemic penumbra following stroke, microarray analysis was performed on cortical tissues from sham, MCAO, and MCAO+NRG1 rats twelve hours after surgery.

Of the total 30,429 gene probes on the Applied Biosystems Rat 2.0st chip, 21,526 genes were annotated for the rat genome. The microarray plots show the relationship between the signal intensity for the expressed genes and difference between two conditions for those genes. The plots in Fig 1A compare the gene intensities of the genes differentially expressed for the sham control and MCAO. Following MCAO, there was a dramatic increase in the number of genes upregulated and downregulated compared to sham. The plots in Fig 1B compare the gene intensities of the genes differentially expressed for the Sham control and MCAO+NRG-1 conditions, featuring a similar increase in the number of genes upregulated and downregulated as in Fig 1A.

When comparing gene expression from the MCAO condition to rats treated with NRG-1 before MCAO (Fig 1C), there were 556 genes which were up and downregulated by NRG-1. The 253 genes that were differentially expressed between the MCAO and NRG-1 groups with a fold change (fc) > 1.5 and p-value < 0.05 were selected for further analysis. In Table 1, genes that underwent separate expression patterns were categorized and clustered based on statistical expression changes.

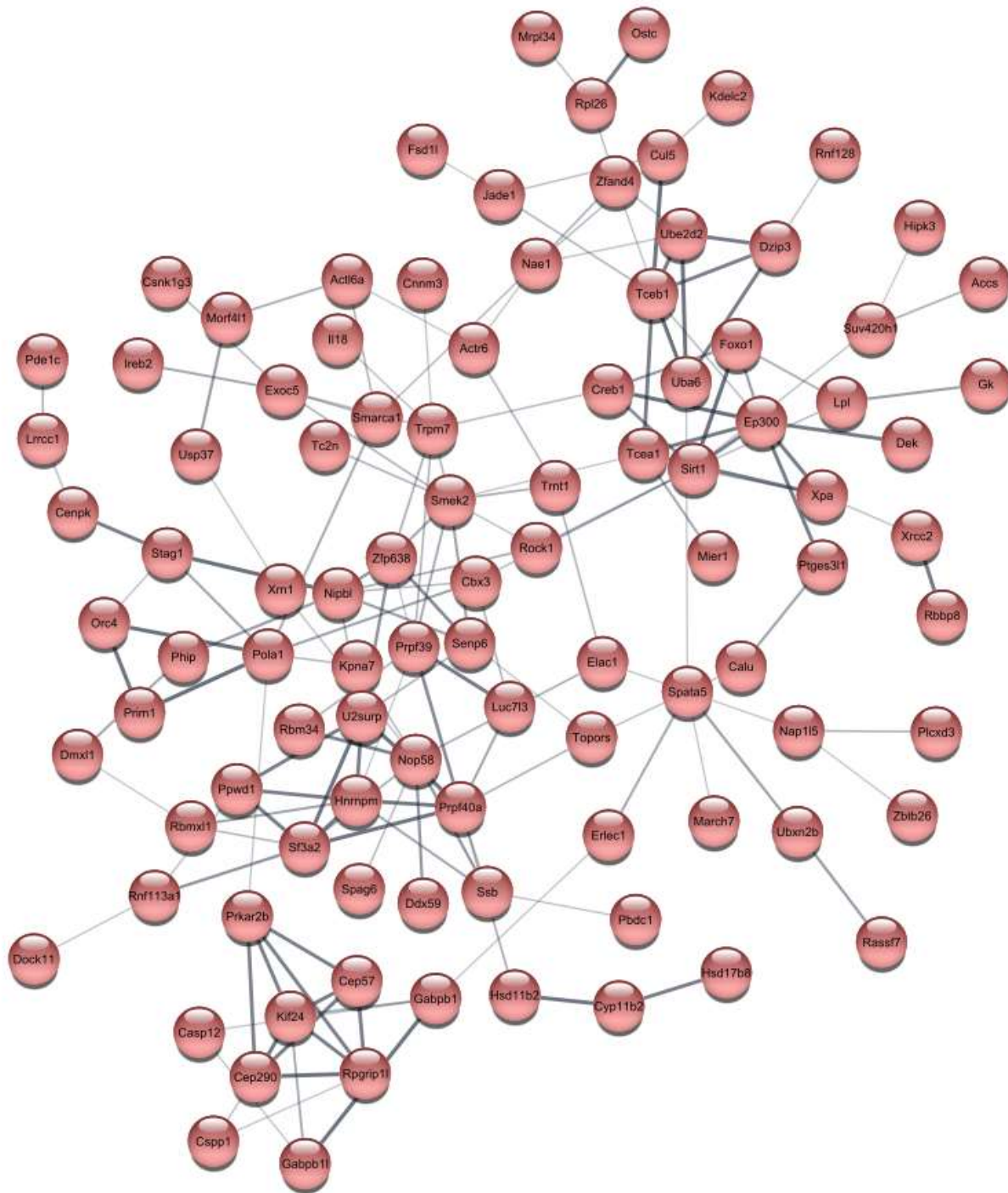


**Fig 1. Differential Gene Expression Analysis.** (a) Overview of genes differentially expressed between the Sham and 12 h MCAO conditions. (b) Overview of genes differentially expressed between the Sham and 12 h NRG conditions. (c) Overview of genes differentially expressed between the 12h MCAO and 12 h NRG conditions. (d) Volcano plot of genes differentially expressed between the 12 h MCAO and 12 h NRG conditions.

There were 26 genes that increased expression with MCAO ( $fc > 1.5$ ) and further increased with NRG-1 ( $fc > 1.5$ ), which are associated with metabolic processes, cellular growth, biological regulation, stimuli response, and localization. These genes are in pathways such as CCKR signaling, cadherin signaling, and cytokine mediated inflammation. Of these genes, two (Eed and Zfp62) are transcription factors. 188 genes whose expression remained unaltered following

**Table 1. Genes with change from SHAM due to MCAO and subsequent significant upregulation due to NRG-1 after 12h.**

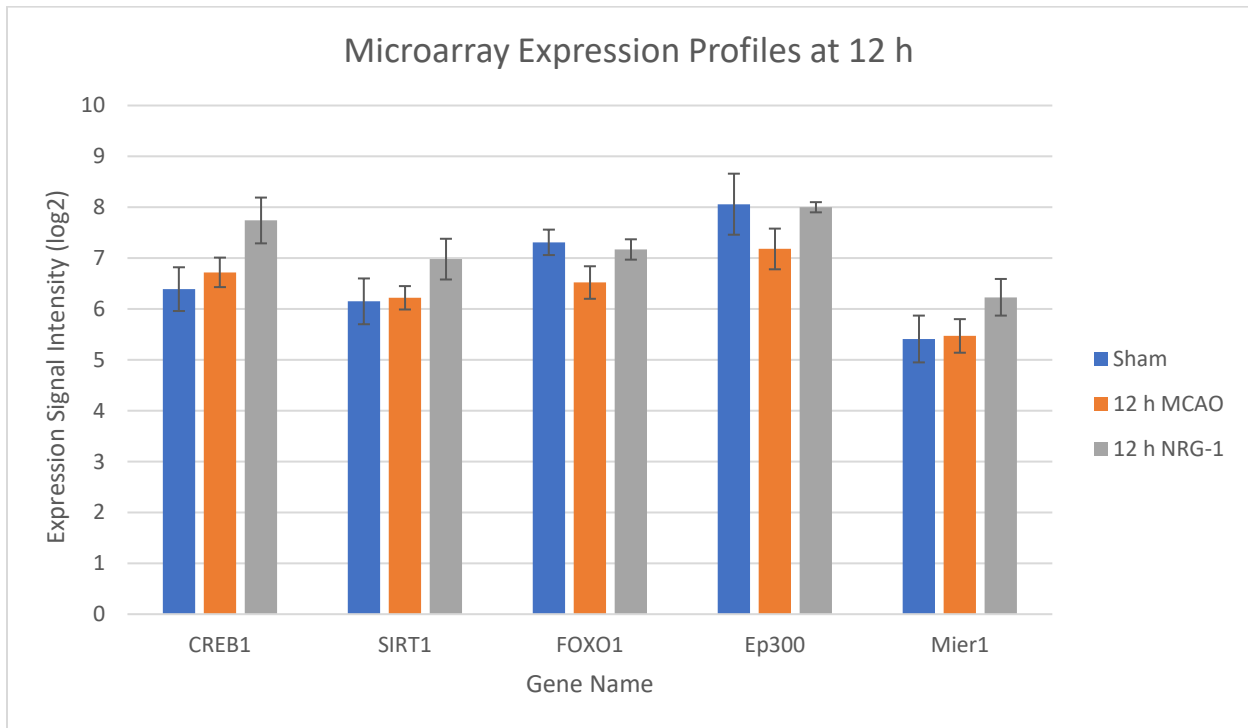
Gene Changes	Gene (n)	Gene Symbols
Genes with increase with MCAO (fc > 1.5) and statistical increase with NRG-1 (fc > 1.5)	26	Tomm70a, Tcea1, Ppwd1, Eed, Tcea8, Thoc7, Nipbl, Sult1d1, Zfp62, Swt1, Hnrnpm, Plcx3, Actr6, Chpt1, Ppp4r3b, Fam135a, Btg3, Ccdc88a, Il18, Cep290, Rock1, Zfp780b, Orc4, Prpf39, Nop58, Nts
Genes maintained with MCAO (1.5 > fc > -1.5) and statistical increase with NRG-1 (fc > 1.5)	188	Mir423, Efcab1, Ccdc171, Pros1, Cbx3, Oste, Smarcal1, Rbm34, Tc2n, Nap115, Bex4, Dppa311, Mum111, Mier1, Xrn1, Sirt1, Suv420h1, Apoo, Actl6a, Ube2d2, Bag4, Zfand4, Morf411, Csp1, Rbbp8, Vom1r7, Zfp458, Diaph2, Spag6, Hgf, Hipk3, Olr1601, Olr1257, Olr1736, Morc4, Dnajc24, Lpl, Plek2, Phip, Dmx11, Dzip3, Lrif1, Vcsa1, Mgat4c, Casp12, Ssb, Mipol1, Spata5, Tatdn1, Tmem251, Olr1214, Lrch2, Slc5a7, Erlec1, Zfp605, Creb1, Ireb2, Stag1, U2surp, Trnt1, Rasa2, Lrrtm2, Kcna4, Calu, Zfp280c, Uba6, Serpinb6, Chmp5, Zfp638, Nbeal1, Pbd1, Nae1, Senp6, Cep57, March7, Apool, Trpm7, Dsel, Dek, Syt10, Zfp280d, Zfp945, Rsb1, Exoc5, Prpf40a, Cul5, Mpp6, Luc7l3, Micu3  Plppr1, Rnf223, Znf354b, Unc13d, Rnf113a1, Hsd17b8, Pxs1, Rassf7, Adora2b, Ddx59, Sdsl, Nek10, Mboat2, Nap112, Slc25a45, Olr1488, Cox19, Zfp420, Prim1, Npy2r, Lrrcc1, Cyp11b2, Kpna7, Hnmt, Slx4ip, Nfkbil1, Ubxn2b, Kazald1, Rnase4, Mei4, Tfdp2, Mcts2, Slc6a18, Strip2, Rpl26, Npy2r, Pus10, Slc25a2, Hic2, Ankdd1b, Lrrn4cl, Fcho2, Ccdc191, Xrcc2, Fbn2, Ces2e, Olr87, Dusp13, Olr1462, Scaper, Slc18a2, Cdca71, Rbm11, Ghr, Timm10b, Olr860, Topors, Xpa, Zfp597, Eci3, Jrkl, Olr777, Ifit1bl, Ptges31l, St8sia4, Kif4b, Fsd11, Epha6, Gabpb1, Il1rap1l, Gk, Pik3r3, Pde1c, Ccdc69, Gabpb1, Ints8, Dock11, Fam133b, Vom1r19, Acp1, Zbtb26, Kctd4, Ly6i, Ccl28, Atp6ap1l, Cenpk, Rc3h1, Rnf128, Pola1, Pts, Csnk1g3, Kif24, Mir181b2, Usp37, Cyp7b1, Snx24, Cmpk1, Prkar2b, Tceb1
Genes with decrease with MCAO (fc < -1.5) and statistical increase with NRG-1 (fc > 1.5)	39	Igkv5-48, Zic2, Cnnm3, Mrpl34, Sf3a2, Ccdc141, Pcdh19, Ebf4, Rwdd3, Eda, Ep300, Olr1313, Cpt1b, Elac1, Pcdhb9, Cdhr1, Pdcl, Foxo1, Dmr1c1b, Smim17, Mir181c, Tmem126b, Jade1, Ndst4, Obp2b, Mir21, Atp6v0a2, Fancg, Accs, Hsd11b2, Zfp867, Echdc2, Kdelc2, Pfkfb2, Slc45a2, Rpgrip1l, Adprh1l, Snapc5, Rslcan18



**Fig 2. Network interaction of genes (n = 99) upregulated with  $fc > 1.5$  between the 12h MCAO and 12h NRG conditions. Protein-protein interactions visualized using STRING are used to identify potential “hub” genes that signify regulatory factors. The thickness of the connecting line represents the confidence interval of the interaction. Orphan genes unconnected to the network were removed from view.**

MCAO ( $-1.5 < fc < 1.5$ ) but then increased following NRG1 ( $fc > 1.5$ ) treatment were associated with metabolic processes, cellular growth, biological regulation, and immune system function.

These genes are in pathways such as oxidative stress response, p53 signaling, DNA replication, PI3K pathway, EGF signaling, and more. Of these genes, fifteen are transcription factors: Pros1, Mier1, Sirt1, Creb1, Zfp280c, Dek, Znf354b, Psx1, Mei4, Hic2, Cdca71, Rbmx11, Xpa, Gabpb1, and Zbtb26. There were 39 genes that decreased expression with MCAO ( $fc < -1.5$ ) and were rescued with NRG-1 ( $fc > 1.5$ ), which are associated with metabolic process, cellular development, cell maintenance, and biological regulation. These genes are in pathways such as CCKR signaling, cadherin signaling, and Insulin/IGF pathway, PI3K pathway, and Wnt signaling. Of these genes, five are transcription factors: Zic2, Ebf4, Ep300, Foxo1, and Mir21.

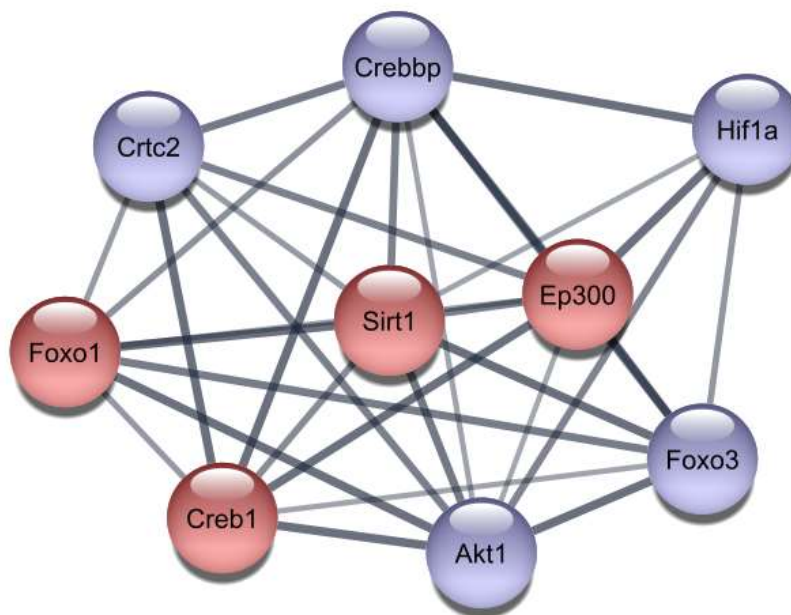


**Fig 3. Gene expression profiles among statistically significant genes (ANOVA,  $p < 0.05$ ) in Sham (n=4), MCAO (n=4), and MCAO+NRG1 (n=5) treated animals at 12 h following injury. FOXO1, Ep300, CREB1, and SIRT1 were shown to be highly interactive with one another, suggesting the regulation of a regulatory pathway with NRG-1 treatment.**



The STRING database was used to understand the relationships between the genes identified the TAC software. STRING allows users to obtain a visualized network of protein-protein interactions from a list of proteins uploaded to the website. All genes listed in Table 1 were uploaded into STRING, as shown in Figure 2. Protein-protein interactions visualized using STRING are used to identify potential “hub” genes that could signify key regulatory factors. The thickness of the connecting lines reflects the confidence interval of the interaction, with darker lines signifying high confidence that the proteins these genes encode interact with one another.

The FOXO1, CREB1, SIRT1, and Ep300 genes displayed high confidence interactions with one another (shown in Figure 2) and had significant microarray expression (shown in Figure 3). These four genes were selected for further analysis. The first five notable interactors of these genes are CREBBP, HIF1A, FOXO3, AKT1, and CRTC2, as shown in an expansion of the network in Figure 4.

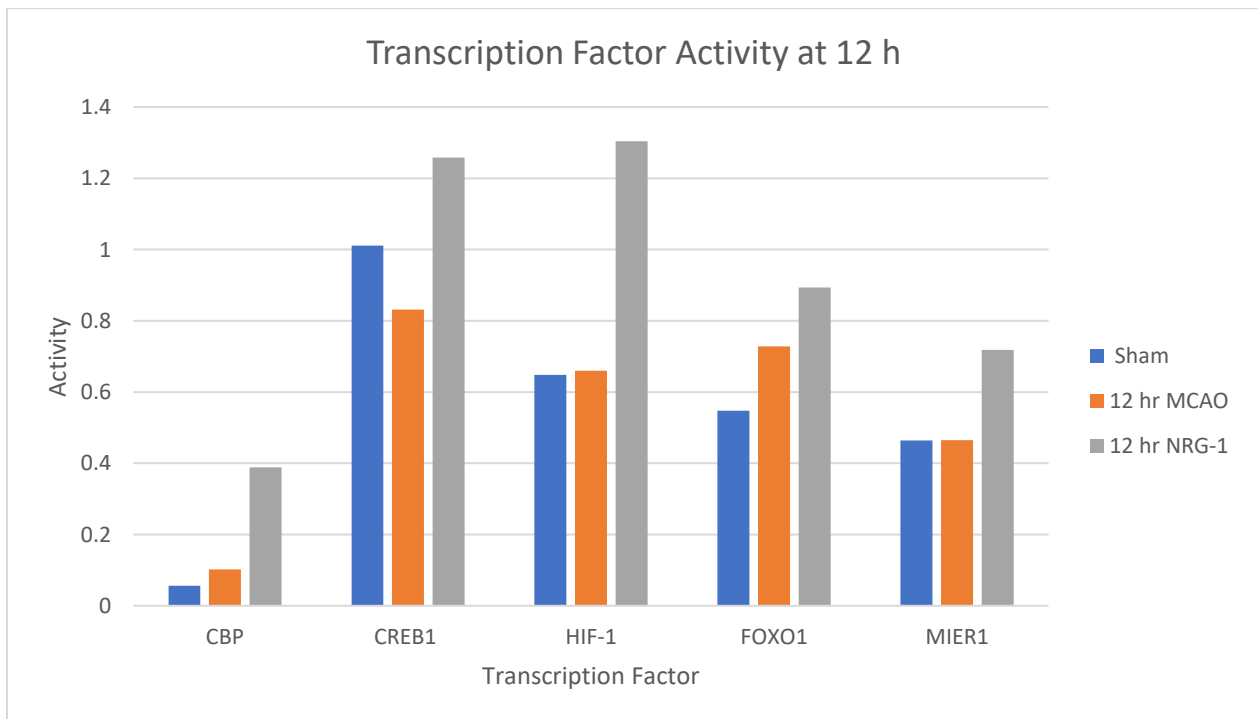


**Fig 4. Protein-protein interactions visualized using STRING was used to expand the network with the first 5 interactors (shown in purple) of the upregulated genes of interest (shown in red) and identify potential pathways involved with these genes.**

### *Multiplex Transcription Factor Array*

To examine whether the predicted transcriptional regulators were involved with ischemia and NRG1 neuroprotection, we conducted multiplex transcription factor assays on nuclear extracts from the brains of control, MCAO, and MCAO+NRG1 animals. Three factors identified by the TAC software analysis were present on the transcription factor array plate, FOXO1, CREB1, and Ep300 (denoted as CBP). Additionally, the HIF-1 transcription factor identified in the expanded network in Figure 4 was also present on the array.

As shown in the transcription factor array in Figure 5, all these factors featured significant activity changes with NRG-1 delivery twelve hours after stroke. CBP and FOXO1 experienced an upwards trend of activity being increased with MCAO and further increased with NRG-1. HIF-1 experienced no change with MCAO, but in the context of both MCAO and NRG-1, activity was



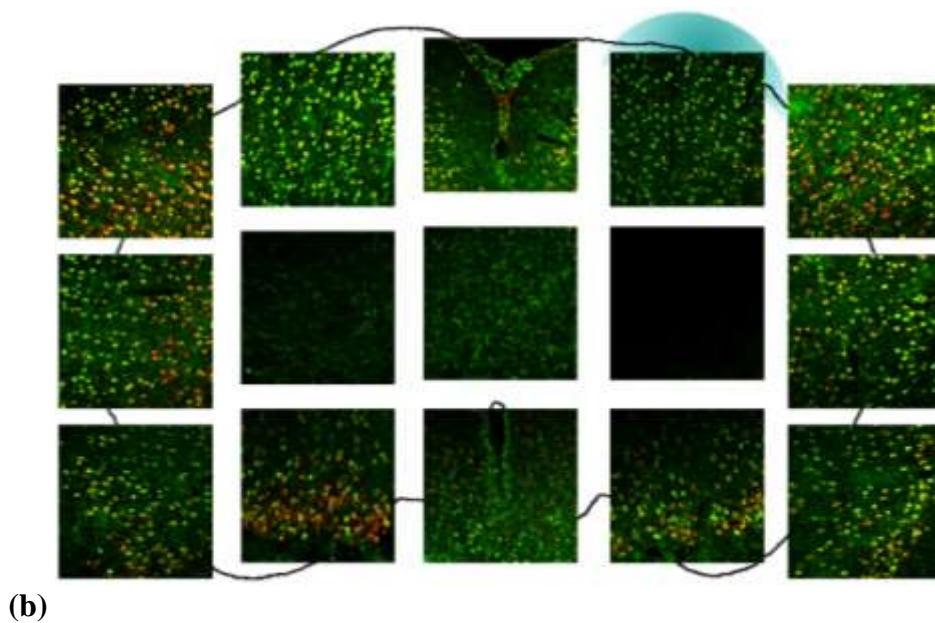
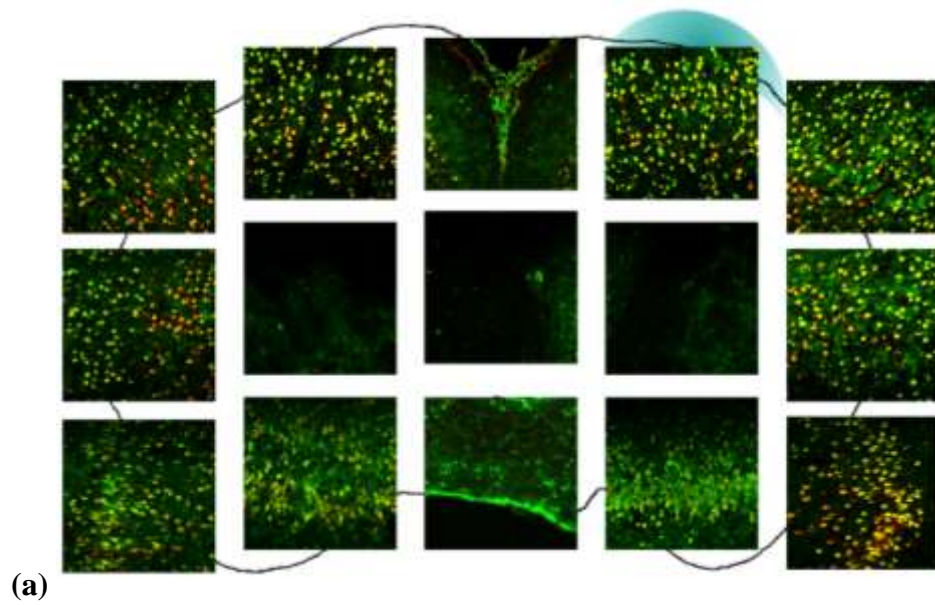
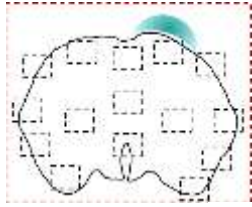
**Fig 5. The activity level of transcription factors is shown in the graph. With NRG1 treatment 12 h after injury, transcription factor activity of CBP, CREB1, HIF1, FOXO1, and MIER1 all increase compared to MCAO.**

increased. CREB1 featured decreased activity with MCAO but was rescued with NRG-1 treatment. The increased activity of these factors due to NRG-1 and the increased microarray expression due to NRG-1 suggest that these factors are in fact being stimulated by NRG-1.

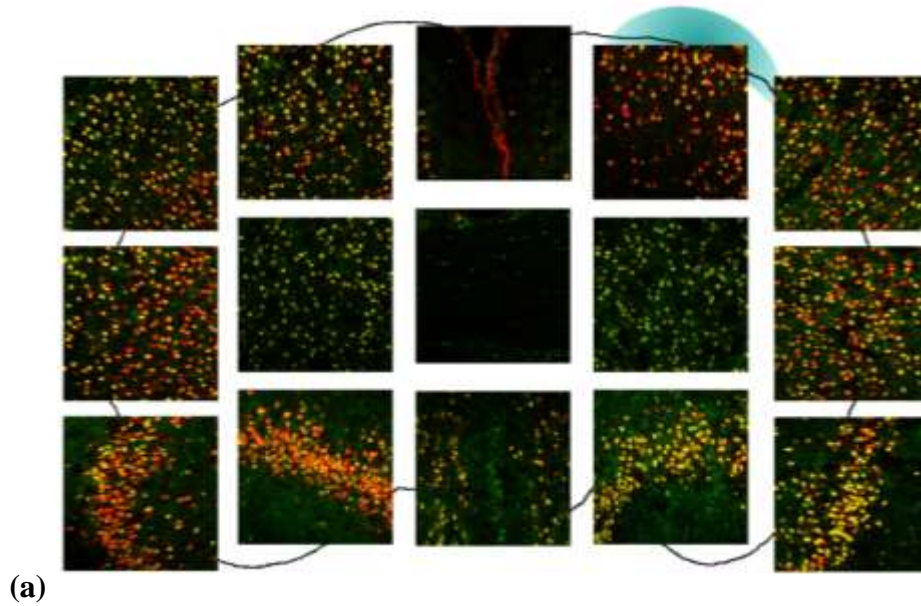
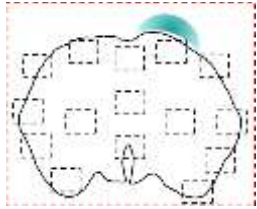
#### *Immunohistochemistry (Incomplete due to COVID-19)*

Immunohistochemistry staining techniques were done to elucidate that types of brain cells involved in NRG-1 delivery responses. PhosphoErbB4 (shown in green) was used to indicate phosphorylated ErbB4 receptors, which receive NRG-1. The NeuN stain was used to image neurons, Iba-1 was used for microglia, and GFAP was used for astrocytes. Slices of both injured and uninjured brains one-hour, two-hours, three-hours, and seven-hours after NRG-1 delivery were meant to be stained. Due to COVID-19 lab personnel restrictions, only neurons of uninjured brain slices were stained at the one-hour, two-hour, three-hour, and seven-hour timepoints.

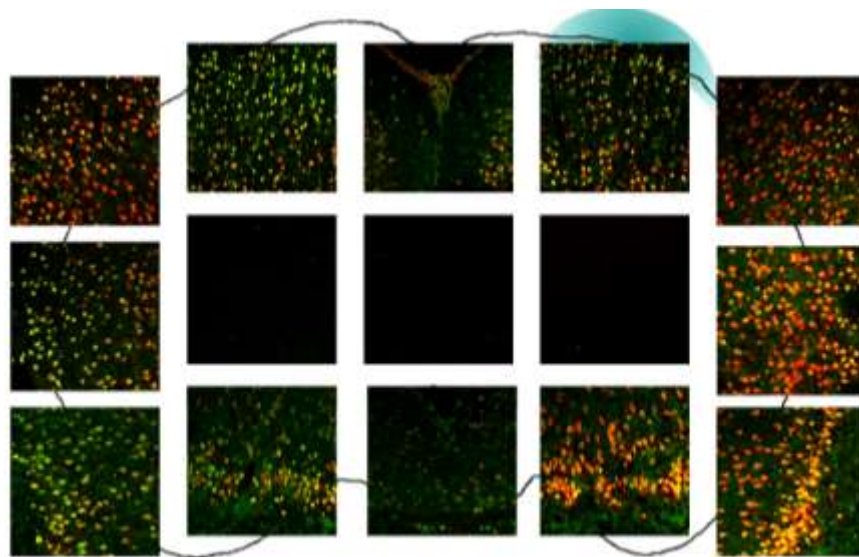
These results showed that three-hours and seven-hours following exogenous NRG-1 treatment on an uninjured brain, neurons have high levels of colocalization with the phosphorylated ErbB4 receptors (shown in Figure 6). The amount of colocalization at the one-hour and two-hour time points is significantly less (shown in Figure 7). Hence, there is a clear progression of colocalization over time. This suggests that even without injury, NRG-1 delivery causes a signaling cascade in neurons and could signify that NRG-1 mediates a response throughout the entire brain rather than just at the local injury point. While immunohistochemistry experiments remain incomplete due to COVID-19, these preliminary results serve as a basis for evaluating ischemic stroke in the future.



**Figure 6.** IHC staining of phosphoErbB4 against NeuN to determine colocalization of phosphorlyated ErbB4 receptors activated by NRG-1 (shown in green) and neurons (shown in red). Levels of colocalization observed by yellow coloring. Hydrogels infused with NRG-1 were placed on exposed brain tissue for (a) 1 hour and (b) 2 hours (delivery site shown in blue). *Some image details courtesy of Jennifer Yang.*



(a)



(b)

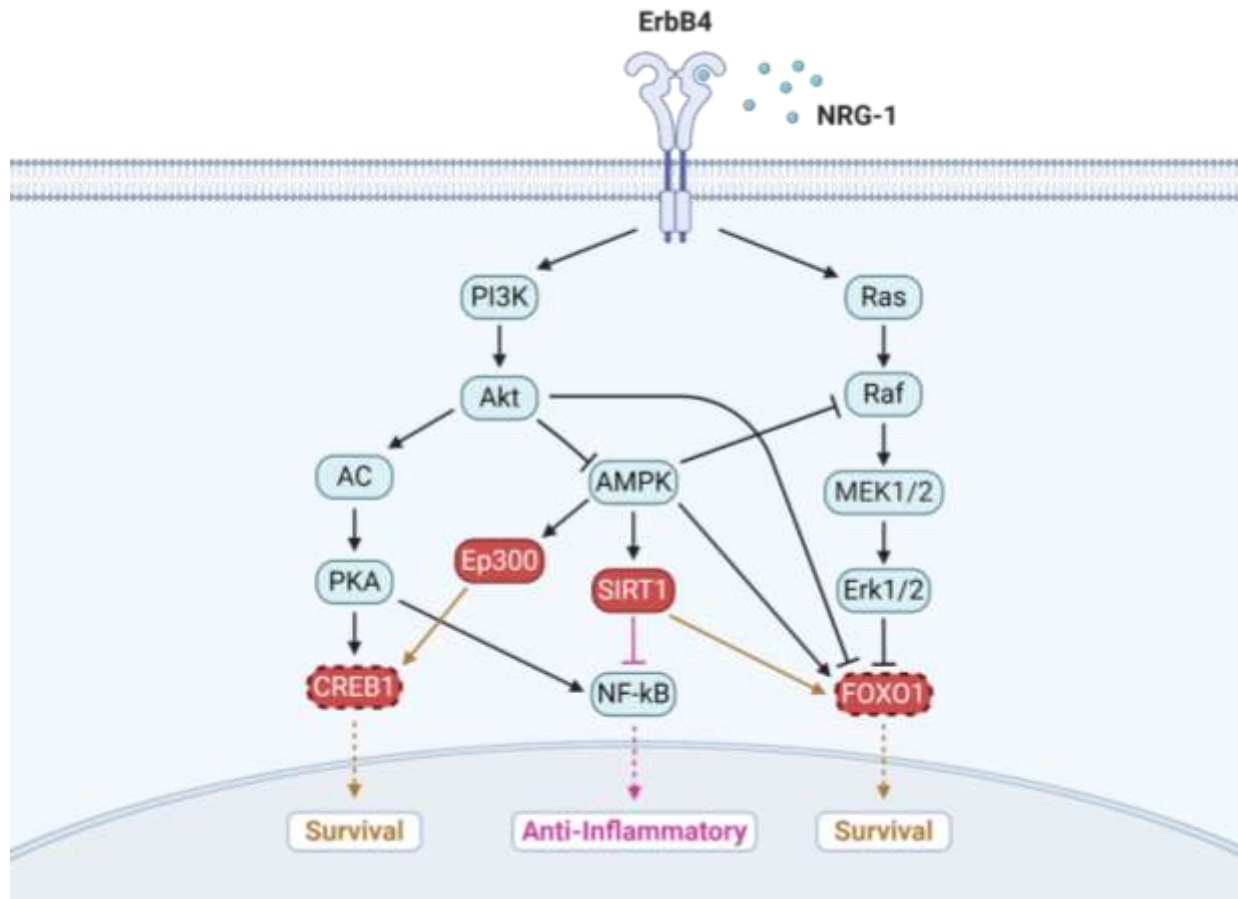
**Figure 7.** IHC staining of phosphoErbB4 against NeuN to determine colocalization of phosphorylated ErbB4 receptors activated by NRG-1 (shown in green) and neurons (shown in red). Levels of colocalization observed by yellow coloring. Hydrogels infused with NRG-1 were placed on exposed brain tissue for (a) 3 hours and (b) 7 hours (delivery site shown in blue). *Some image details courtesy of Jennifer Yang.*

## DISCUSSION

Neuregulin-1 has demonstrated neuroprotective properties in rats following ischemic stroke. These properties have been associated with the regulation of inflammatory gene expression. The regulation of inflammatory responses by NRG-1 in ischemia has been previously reported by our lab to involve the NF- $\kappa$ B and PI3K-AKT signaling pathways (16); however, the molecular mechanisms and the exact genes involved in Neuregulin-1 neuroprotection remains unclear.

Microarray analysis of rat brain tissue was done to elucidate the regulatory effects on gene expression that NRG-1 delivery has on ischemic brains twelve hours after injury. Of the total 30,463 genes analyzed, 565 genes were significantly expressed between the MCAO and MCAO+NRG1 groups. These genes have been associated with anti-inflammatory and pro-survival pathways, such as the PI3K-AKT pathway, which plays a key role in regulating cell proliferation, differentiation, apoptosis, and migration (17).

In this study, differential gene expression of downstream targets of the PI3K-AKT signaling pathway were identified. The expression of several genes related to the regulation of inflammation and oxidative stress were increased. Namely, the delivery of exogenous Neuregulin-1 resulted in the upregulation of the CREB1 and FOXO1 transcription factors, both downstream of the PI3K-AKT pathway. CREB1, a cAMP responsive element binding protein activated by the Ep300 protein, is a transcription factor that drives several cellular responses, such as cell proliferation, survival, and differentiation. CREB1 has been identified in having specific immune functions, including inhibiting canonical NF- $\kappa$ B pro-inflammatory activation, inducing macrophage survival, and promoting the proliferation, survival, and regulation of T and B lymphocytes (18). FOXO1, a forkhead box protein, has been reported to regulate apoptosis and



**Fig 8. Pathway analysis of NRG-1 neuroprotection and involvement in the PI3K-AKT pathway. Gene upregulated with NRG-1 delivery compared to MCAO, shown in red, have been associated with pro-survival and anti-inflammatory response.**

oxidative stress downstream of AKT in neurons. Additionally, the expression level of SIRT1, a nicotinamide adenosine dinucleotide-dependent histone deacetylase downstream of the PI3K-AKT pathway, was upregulated in this dataset. SIRT1 is a transcriptional factor that plays a role in longevity, apoptosis, and stress resistance by deacetylating proteins, such as p53, NF-κB, and FOXO transcription factors (19). Through deacetylation, SIRT1 has been shown to regulate the transcriptional activity of NF-κB and protect cells from p53-induced apoptosis (20,21). SIRT1 promotes FOXO1-induced cell cycle arrest, but inhibits FOXO1-induced cell death (22,23).

The CREB1, FOXO1, and SIRT1 transcription factors play roles in cell survival following ischemic stroke that are heavily interconnected and dependent upon one another (Figure 8). Their increased microarray expression following NRG-1 delivery and increase in transcriptional regulation activity hint at the activation of the PI3K-AKT pathway and its importance in ischemic stroke. Further research on these genes is necessary to elucidate the mechanisms of NRG-1 neuroprotection.

## CONCLUSION

Neuroprotectant treatments aimed at preventing neuronal death within the three to twenty-four hour window have gone mostly unexplored. NRG-1 has been shown to affect mechanisms that occur several hours after stroke, signifying its potential for usage in an extended therapeutic window. These findings suggest that neuregulin-1 influences pro-survival and anti-inflammatory gene expression, providing novel insight into the molecular mechanisms involved in neuregulin-1 neuroprotection.

Due to the complexity of the tissue samples used in the microarray and transcription factor array, future studies utilizing alternate approaches that are region specific are needed. With a homogenization of tissue, it is unclear whether NRG-1 is rescuing tissue over time, which could both impact the signals seen at later time points. The coupling between tissue morphology and gene expression has gone unmeasured, emphasizing the need for new methods that can distinguish expression between the necrotic core and penumbra. Future work will utilize the novel Digital Spatial Profiling technique to evaluate gene expression in a regional manner.



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SUPPLEMENTARY

**Supplemental 1: Table of Microarray Data for all genes that were significantly regulated (12h MCAO vs 12h NRG-1 Fold Change > 1.5) between injury and treatment conditions.**

Gene Symbol	Sham (log2)	Sham STD	12h MCAO (log2)	12h MCAO STD	12h NRG (log2)	12h NRG STD	12h MCAO vs Sham P-val	12h NRG vs Sham P-val	12h MCAO vs Sham Fold Change	12h NRG vs Sham Fold Change
Abca2	9.72	0.14	9.03	0.44	8.39	0.76	0.0052	1.45E-05	-1.61	-2.51
Accs	4.12	0.11	3.47	0.36	4.1	0.2	0.0050	0.8970	-1.57	-1.02
Acnat1	2.6	0.25	2.96	0.43	2.26	0.28	0.0983	0.1153	1.29	-1.26
Acot3	5.62	0.28	5.27	0.47	4.62	0.25	0.0984	0.0001	-1.28	-2
Acp1	3.52	0.38	5.28	0.35	4.03	0.49	0.9092	0.0130	-1.1	1.43
Acta1	5.77	0.32	5.29	0.42	4.92	0.32	0.8729	0.0039	-1.15	-1.81
Actl6a	4.95	0.21	5.30	0.2	5.7	0.5	0.5757	0.0006	1.07	1.69
Actr6	6.27	0.37	5.31	0.38	7.79	0.61	0.0054	1.27E-06	1.81	2.87
Adamts4	5.92	0.21	5.32	0.57	5.95	0.66	0.0107	0.8952	1.69	1.02
Adgrl1	9.67	0.12	5.33	0.35	8	0.24	5.53E-07	5.88E-10	-1.93	-3.19
Adh6	2.81	0.18	5.34	0.52	2.73	0.14	0.0666	0.5044	1.47	-1.05
Adora2b	6.3	0.25	5.35	0.19	6.42	0.18	0.0016	0.5578	-1.45	1.09
Adprhl1	4.64	0.07	5.36	0.35	4.75	0.16	0.0054	0.5294	-1.51	1.07
Akr1b8	2.3	0.22	5.37	0.35	2.31	0.52	0.0030	0.1856	1.87	1.01
Akt1s1	7.27	0.06	5.38	0.25	6.16	0.25	0.0029	8.56E-07	-1.38	-2.16
Amy2a3	2.82	0.23	5.39	0.71	2.88	0.39	0.0143	0.5578	1.6	1.04
Anapc2	7.62	0.25	5.40	0.21	6.11	0.33	0.0001	9.86E-08	-1.81	-2.83
Angptl4	5.1	0.23	5.41	0.63	5.4	0.97	9.64E-05	0.1224	3.72	1.23
Ankdd1b	3.02	0.08	5.42	0.27	3.3	0.26	0.2692	0.1656	-1.27	1.21
Ankrd34a	8.65	0.11	5.43	0.21	6.69	0.8	2.04E-05	1.64E-08	-2.44	-3.89
Ankrd34c	4.89	0.39	5.44	0.3	4.25	0.68	0.4511	0.0342	1.18	-1.56
Ankrd54	5.16	0.28	5.45	0.3	4.87	0.38	0.2469	0.0532	1.29	-1.21
Ankrd65	4.15	0.49	5.46	0.29	4.05	0.16	0.0328	0.4495	1.45	-1.07
Apln	6.6	0.12	5.47	0.2	6.02	0.39	0.6449	0.0128	1.03	-1.49
Apoo	6.76	0.25	5.48	0.16	7.71	0.46	0.8304	0.0037	1.06	1.93
Apool	4.5	0.58	5.49	0.28	5.61	0.61	0.4091	0.0019	1.37	2.17
Arhgap31	6.47	0.07	5.50	0.46	6.18	0.59	0.0489	0.2713	1.36	-1.23

Atat1	7.92	0.1	5.51	0.55	6.58	0.53	0.0043	8.18E-06	-1.47	-2.54
Atg2a	7.15	0.18	5.52	0.28	5.17	0.59	5.66E-06	3.11E-09	-2.55	-3.93
Atp6ap11	6.7	0.42	5.53	0.74	7.35	0.3	0.3702	0.1224	-1.06	1.57
Atp6v0a2	7.2	0.2	5.54	0.35	6.57	0.44	0.3181	0.0033	1.05	-1.55
Atp6v0a2	4.93	0.29	5.55	0.35	4.99	0.57	0.0038	0.5998	-1.6	1.04
Bag4	7.61	0.44	5.56	0.62	8.32	0.42	0.9923	0.0062	1.08	1.64
Bdnf	5.93	0.27	5.57	0.41	6.91	0.39	1.24E-06	0.0002	3.21	1.97
Bex4	4.48	0.44	5.58	0.46	5.63	0.34	0.8681	0.0006	1.04	2.22
Bgn	7.91	0.17	5.59	0.41	6.53	0.84	0.0356	6.70E-05	-1.6	-2.61
Bin1	9.85	0.06	5.60	0.33	8.31	0.47	0.0009	8.71E-07	-1.58	-2.9
Btg3	5.74	0.48	5.61	0.25	7.37	0.51	0.0006	2.66E-07	1.88	3.1
Calu	6.67	0.37	5.62	0.31	7.67	0.25	0.0407	9.21E-06	1.29	2
Capns1	10.36	0.41	5.63	0.48	9.16	0.51	0.0146	4.96E-05	-1.34	-2.3
Car9	4.16	0.13	5.64	0.18	3.88	0.31	0.0623	0.7272	1.32	-1.21
Casp12	3.28	0.16	5.65	0.3	4.27	0.42	0.0861	1.58E-05	1.19	1.98
Casp14	2.95	0.28	5.66	0.33	2.91	0.38	0.0081	0.4663	1.46	-1.03
Catsper1	2.75	0.23	5.67	0.21	2.69	0.28	0.0036	0.9997	1.5	-1.04
CB741658	3.45	0.21	5.68	0.4	3.58	0.21	0.0039	0.3604	1.68	1.09
Cbx3	7.25	0.46	5.69	0.59	8.21	0.46	0.2138	0.0013	1.02	1.94
Ccdc32	7.45	0.33	5.70	0.33	7.24	0.42	0.2667	0.0527	1.4	-1.16
Ccdc69	3.7	0.54	5.71	0.29	4.18	0.37	0.2136	0.3437	-1.13	1.39
Ccdc88a	7.38	0.53	5.72	0.39	9.05	0.24	0.0009	7.03E-07	1.95	3.18
Ccdc115	6.73	0.24	5.73	0.44	6.38	0.38	0.4027	0.0608	1.2	-1.27
Ccdc141	5.21	0.54	5.74	0.49	5.09	0.43	6.69E-06	0.0147	-2.28	-1.09
Ccdc171	5.75	0.43	5.75	0.49	6.44	0.63	0.8335	0.0185	1.01	1.61
Ccdc191	4.06	0.28	5.76	0.21	4.4	0.16	0.2015	0.0639	-1.25	1.26
Cckbr	7.91	0.28	5.77	0.63	6.9	0.35	0.0249	8.46E-05	-1.16	-2.03
Ccl7	4.1	0.23	5.78	0.76	6.83	0.27	1.90E-12	3.26E-10	11.73	6.65
Ccl28	3.73	0.34	5.79	0.15	4.24	0.46	0.4307	0.1708	-1.07	1.43
Cd74	7.33	0.22	5.80	0.56	6.98	0.35	0.3088	0.3156	1.18	-1.28
Cd82	7.04	0.09	5.81	0.33	6.68	0.52	0.0393	0.6740	1.49	-1.28
Cd207	2.95	0.12	5.82	0.35	2.85	0.15	0.0221	0.6160	1.5	-1.07
Cdc42ep1	6.47	0.08	5.83	0.28	5.22	0.42	0.0033	4.99E-06	-1.44	-2.38

Cdca7l	3.71	0.33	5.84	0.41	4.54	0.37	0.6984	0.0002	-1.22	1.78
Cdhr1	6.12	0.29	5.85	0.11	5.91	0.48	0.0011	0.1990	-1.75	-1.16
Celf3	8.36	0.09	5.86	0.6	6.14	0.33	1.18E-08	2.26E-11	-2.72	-4.64
Cenpk	3.64	0.29	5.87	0.44	4.18	0.56	0.8866	0.0041	-1.06	1.45
Cenpw	4.59	0.25	5.88	0.34	4.81	0.27	0.0041	0.5270	1.83	1.16
Cep57	5.54	0.64	5.89	0.67	7.05	0.66	0.1372	0.0001	1.36	2.86
Cep290	5.5	0.53	5.90	0.46	7.14	0.34	0.0045	1.15E-05	1.97	3.13
Ces2e	2.89	0.14	5.91	0.41	3.15	0.17	0.1686	0.1464	-1.25	1.2
Chchd4	5.72	0.39	5.92	0.22	5.32	0.38	0.2107	0.3289	1.23	-1.32
Chkb; Cpt1b	5.94	0.03	5.93	0.54	5.68	0.34	0.0024	0.3253	-1.8	-1.2
Chmp5	6.04	0.59	5.94	0.2	7.28	0.32	0.1375	1.95E-05	1.33	2.36
Chpt1	6.1	0.57	5.95	0.18	7.74	0.52	0.0399	2.16E-05	1.85	3.1
Cish	6.23	0.2	5.96	0.4	5.11	0.65	0.3876	0.0009	-1.25	-2.17
Ciz1	7.3	0.21	5.97	0.55	6.18	0.36	0.1533	0.0001	-1.12	-2.18
Clic5	6.16	0.15	5.98	0.15	5.57	0.33	0.3387	0.0001	1.1	-1.51
Cmklr1	4.87	0.31	5.99	0.5	4.84	0.2	0.0176	0.8557	1.68	-1.02
Cmpk1	6.81	0.37	5.100	0.38	7.46	0.56	0.5607	0.0017	-1.01	1.58
Cnih3	7.1	0.17	5.101	0.38	5.28	0.52	0.0002	2.37E-07	-2.3	-3.54
Cnnm3	6.28	0.4	5.102	0.64	5.25	0.18	3.80E-08	0.0001	-3.15	-2.04
Cntn2	7.54	0.08	5.103	0.36	6.61	0.72	0.3107	0.0004	-1.08	-1.91
Cox19	4.43	0.33	5.104	0.55	4.61	0.28	0.0619	0.4535	-1.41	1.13
Crb1	3.5	0.2	5.105	0.32	3.66	0.16	0.0001	0.2722	1.9	1.12
Creb1	6.39	0.43	5.106	0.29	7.74	0.45	0.4631	0.0024	1.26	2.55
Crtac1	7.86	0.12	5.107	0.29	7.15	0.33	0.7805	0.0008	1.05	-1.64
Csnk1g3	7.01	0.33	5.108	0.33	7.6	0.1	0.4421	0.0139	-1.04	1.5
Cspp1	4.77	0.4	5.109	0.06	5.48	0.23	0.7687	0.0252	1.09	1.64
Csrnp2	6.8	0.2	5.110	0.56	5.25	0.55	0.0442	5.87E-05	-1.43	-2.92
Csrp1	9.96	0.34	5.111	0.3	8.79	0.59	0.0409	0.0001	-1.43	-2.24
Cts8l1	2.3	0.13	5.112	0.33	2.44	0.49	0.0002	0.1099	2	1.1
Cul5	7.47	0.45	5.113	0.43	8.71	0.41	0.0294	3.38E-05	1.47	2.38
Cx3cl1	11.64	0.17	5.114	0.35	9.89	0.59	0.0010	1.98E-07	-1.96	-3.36
Cyb5r3	9	0.25	5.115	0.34	8.1	0.4	0.0441	0.0001	-1.21	-1.86
Cyb561a3	4.42	0.58	5.116	0.43	3.72	0.34	0.8075	0.0032	1.32	-1.63
Cyp2s1	5.57	0.19	5.117	0.46	4.92	0.41	0.6962	0.0145	1.21	-1.57
Cyp7b1	6.45	0.45	5.118	0.06	7.08	0.55	0.7071	0.0462	-1.02	1.55
Cyp11b2	3.6	0.14	5.119	0.32	3.73	0.44	0.1687	0.1719	-1.37	1.1

Dcaf4	7.41	0.29	5.120	0.41	5.88	0.61	0.0076	8.40E-06	-1.66	-2.88	
Dcaf5	7.91	0.1	5.121	0.47	6.28	0.49	0.0001	2.61E-07	-1.69	-3.09	
Dcp1a	6.37	0.14	5.122	0.52	5.33	0.56	0.2023	0.0007	-1.2	-2.05	
Ddx59	5.09	0.11	5.123	0.55	5.65	0.37	0.1941	0.1599	-1.44	1.48	
Defb50	2.81	0.21	5.124	0.26	2.71	0.5	0.0097	0.5553	1.5	-1.08	
Dek	7.44	0.39	5.125	0.33	8.61	0.44	0.0072	2.96E-06	1.41	2.26	
Dhrs3	7.15	0.09	5.126	0.36	5.71	0.47	0.0006	3.79E-07	-1.75	-2.72	
Diaph2	5.71	0.24	5.127	0.29	6.53	0.43	0.7833	0.0072	1.1	1.77	
Dmrtc1b	6.41	0.27	5.128	0.29	6.27	0.38	0.0025	0.4735	-1.71	-1.1	
Dmx11	7.7	0.31	5.129	0.24	8.67	0.37	0.4718	0.0007	1.15	1.96	
Dnajb5	8.15	0.15	5.130	0.27	7.78	0.43	0.0941	0.2684	1.25	-1.29	
Dnajc14	6.52	0.27	5.131	0.66	5.57	0.17	0.4822	3.37E-05	1.11	-1.94	
Dnajc24	5.23	0.36	5.132	0.43	6.26	0.35	0.8662	7.41E-05	1.14	2.05	
Dock11	4.48	0.28	5.133	0.07	5.04	0.38	0.1462	0.0233	-1.1	1.47	
Dppa311	4.01	0.28	5.134	0.39	4.69	0.37	0.3590	0.0038	1.04	1.61	
Dsel	4.89	0.41	5.135	0.62	6.17	0.59	0.2010	0.0007	1.39	2.43	
Dusp5	5.63	0.32	5.136	0.75	6.36	0.84	0.0004	0.1183	3.42	1.66	
Dusp13	3.53	0.33	5.137	0.16	3.91	0.38	0.2219	0.0261	-1.24	1.3	
Dym	8.44	0.14	5.138	0.22	7.21	0.38	0.0069	2.72E-06	-1.48	-2.35	
Dzip3	6.92	0.44	5.139	0.29	7.75	0.17	0.6245	0.0011	1.15	1.78	
Ebf4	5.04	0.39	5.140	0.19	4.76	0.17	0.0871	1.36E-06	-2.01	-1.21	
Ece1	7.57	0.08	5.141	0.44	7.14	0.38	0.3373	0.1731	1.16	-1.35	
Echdc2	5.9	0.25	5.142	0.32	5.86	0.35	0.0185	0.5549	-1.57	-1.03	
Eci3	4.51	0.3	5.143	0.66	4.94	0.65	0.4971	0.1447	-1.18	1.35	
Eda	5.21	0.31	5.144	0.4	5.04	0.3	0.0005	0.1146	-1.87	-1.12	
Eed	5.7	0.36	5.145	0.45	6.99	0.46	0.0155	2.44E-05	1.57	2.44	
Efcab1	3.89	0.35	5.146	0.56	4.63	0.41	0.9192	0.0184	1.01	1.67	
Elac1	6.27	0.37	5.147	0.44	6.14	0.39	0.0127	0.5324	-1.78	-1.09	
Elf4	4.67	0.33	5.148	0.41	4.34	0.11	0.0074	0.0762	1.55	-1.26	
Eln	5.47	0.3	5.149	0.52	3.99	0.47	0.05	7.28E-05	1.37E-07	-1.69	-2.79
Endov	5.76	0.19	5.150	0.32	5.19	0.29	0.8282	0.0048	1.04	-1.49	
Ep300	8.06	0.6	5.151	0.4	8	0.1	0.0211	0.9963	-1.84	-1.05	
Epha6	6.75	0.29	5.152	0.33	7.14	0.26	0.1917	0.2568	-1.15	1.31	
Epor	4.75	0.24	5.153	0.13	4.31	0.64	0.5374	0.1201	1.11	-1.36	
Erlec1	7.19	0.65	5.154	0.26	8.16	0.46	0.3245	0.0009	1.25	1.97	

Etl4	8.61	0.25	5.155	0.62	6.31	0.58	8.70E-06	1.05E-08	-2.82	-4.91
Etv3	5.8	0.26	5.156	0.66	5.11	0.5	0.9384	0.0561	1.06	-1.61
Evalc	4.03	0.14	5.157	0.41	3.96	0.56	0.0984	0.7579	1.45	-1.05
Exoc5	7.32	0.31	5.158	0.34	8.51	0.32	0.0092	5.80E-06	1.45	2.28
F2rl2	4.31	0.19	5.159	0.25	4.09	0.44	0.0044	0.4497	1.6	-1.16
Fam13c	6.94	0.17	5.160	0.53	6.82	0.22	0.0050	0.6915	1.47	-1.09
Fam29a	4.49	0.15	5.161	1.1	6.52	0.66	5.02E-07	6.76E-05	11.33	4.08
Fam64a	3.64	0.24	5.162	0.47	3.67	0.16	0.0017	0.8124	1.55	1.02
Fam133b	6	0.38	5.163	0.47	6.57	0.52	0.6611	0.0443	-1.1	1.49
Fam135a	6.56	0.33	5.164	0.41	8.55	0.46	0.0039	1.83E-06	1.88	3.98
Fam227b	3.22	0.26	5.165	0.54	2.93	0.46	0.0230	0.7639	1.45	-1.22
Fancg	3.97	0.17	5.166	0.09	4.1	0.27	0.0004	0.7544	-1.6	1.09
Farp1	7.47	0.16	5.167	0.3	6.15	0.35	9.69E-05	6.13E-08	-1.64	-2.5
Fbn2	4.85	0.25	5.168	0.23	5.21	0.27	0.0499	0.3151	-1.25	1.29
Fbxo46	6.3	0.22	5.169	0.41	5.3	0.14	0.0048	1.91E-06	-1.3	-1.99
Fcho2	6.21	0.48	5.170	0.12	6.67	0.23	0.1832	0.0392	-1.26	1.37
Flnc	4.68	0.39	5.171	0.53	5.01	0.52	2.74E-05	0.0475	2.83	1.25
Flt3	6.59	0.24	5.172	0.19	5.26	0.34	0.0046	6.92E-07	-1.61	-2.51
Foxo1	7.31	0.25	5.173	0.2	7.17	0.32	0.0004	0.3609	-1.73	-1.1
Foxred1	5.26	0.09	5.174	0.54	4.67	0.2	0.3413	0.0045	1.03	-1.51
Frmpd1	6.13	0.11	5.175	0.45	5.39	0.6	0.0630	0.1758	1.39	-1.67
Fsd1	7.62	0.19	5.176	0.11	5.85	0.58	0.0200	1.32E-06	-1.65	-3.41
Fsd11	5.59	0.39	5.177	0.22	6.09	0.44	0.7567	0.0124	-1.15	1.42
Fxyd7	9.31	0.06	5.178	0.41	7.01	0.6	5.40E-06	7.70E-09	-2.52	-4.93
Fzr1	7.49	0.17	5.179	0.12	6.17	0.42	0.0027	3.17E-07	-1.63	-2.49
Gabpb1	4.18	0.36	5.180	0.34	4.94	0.17	0.7138	1.89E-05	-1.12	1.69
Gabpb1l	5.5	0.33	5.181	0.53	6.2	0.46	0.3612	0.0002	-1.15	1.62
Gal	4.03	0.15	5.182	0.4	4.84	0.32	8.22E-07	0.0006	2.68	1.75
Galnt6	5.58	0.12	5.183	0.33	5.54	0.44	0.0065	0.9335	1.75	-1.02
Gamt	7.38	0.05	5.184	0.3	7.09	0.14	0.3076	0.1645	1.25	-1.23
Gem	5.05	0.27	5.185	0.56	6.56	0.48	2.57E-08	5.14E-05	5.14	2.85
Gfra2	8.5	0.34	5.186	0.78	6.9	0.66	0.0038	8.59E-06	-1.46	-3.03

Gga1	8.08	0.19	5.187	0.57	6.05	0.44	9.97E-05	2.59E-08	-2.13	-4.1
Ghr	4.47	0.32	5.188	0.12	4.84	0.44	0.5108	0.0116	-1.21	1.29
Gk	5.73	0.41	5.189	0.41	6.16	0.26	0.4180	0.0916	-1.14	1.35
Gm8369	2.38	0.13	5.190	0.25	2.31	0.17	0.0036	0.4630	1.49	-1.05
Gm8973	3.04	0.24	5.191	0.72	2.9	0.15	0.0888	0.2948	1.48	-1.1
Gm10644	8.19	0.33	5.192	0.45	6.42	0.47	0.0081	1.45E-06	-1.92	-3.4
Gpc6	5.61	0.25	5.193	0.21	5.04	0.33	0.7951	0.0149	1.03	-1.48
Gpd1	8.82	0.09	5.194	0.34	9.2	0.74	0.0004	0.1814	2.55	1.3
Gpr108	6.67	0.13	5.195	0.36	5.53	0.35	0.0099	1.40E-06	-1.46	-2.21
Gpr173	5.74	0.09	5.196	0.4	4.49	0.37	0.0023	9.24E-07	-1.56	-2.36
Gprc5a	3.36	0.26	5.197	0.4	3.65	0.79	0.0010	0.2282	2.47	1.23
Grasp	6.84	0.25	5.198	0.52	6.25	0.39	0.7774	0.0080	1.14	-1.5
Hgf	3.89	0.36	5.199	0.35	4.64	0.5	0.6509	0.0026	1.12	1.68
Hic2	4.86	0.19	5.200	0.39	5.17	0.34	0.0605	0.3944	-1.27	1.23
Hipk3	8.06	0.43	5.201	0.27	9.12	0.37	0.6057	0.0003	1.12	2.1
Hist2h2aa3	5.47	0.37	5.202	0.13	3.96	0.35	0.0069	8.16E-06	-1.72	-2.84
Hnmt	5.6	0.56	5.203	0.21	5.91	0.75	0.2200	0.3310	-1.37	1.24
Hnrnpm	7.16	0.52	5.204	0.36	8.55	0.22	0.0045	2.25E-06	1.68	2.61
Hoxa1	3.06	0.14	5.205	0.28	2.79	0.32	0.0885	0.7971	1.33	-1.2
Hpca	11.07	0.14	5.206	0.43	9.6	0.46	0.0011	2.39E-06	-1.56	-2.78
Hs3st2	6.92	0.23	5.207	0.31	6.53	0.4	0.0164	0.0631	1.56	-1.31
Hs6st1	7.47	0.05	5.208	0.45	6	0.46	0.0002	3.23E-07	-1.72	-2.78
Hsd11b2	4.37	0.29	5.209	0.42	4.4	0.21	0.0785	0.4603	-1.57	1.02
Hsd17b8	5.51	0.18	5.210	0.11	5.62	0.39	0.0027	0.8774	-1.46	1.07
Hspb1	5.26	0.24	5.211	0.31	8.2	0.43	8.71E-13	1.11E-10	12.89	7.69
Ifit1bl	4.3	0.25	5.212	0.39	4.88	0.48	0.2648	0.0643	-1.17	1.49
Ifna1	2.58	0.36	5.213	0.53	2.54	0.25	0.0151	0.6521	1.6	-1.03
Igfals	3.43	0.34	5.214	0.34	2.92	0.46	0.0037	0.2199	1.49	-1.42
Igfl3	3.85	0.16	5.215	0.22	3.55	0.35	0.0572	0.4095	1.27	-1.23
Igkv5-48	6.27	0.69	5.216	0.3	5.51	0.44	0.0003	0.0587	-3.31	-1.69
Igsf9b	7.08	0.03	5.217	0.39	6.61	0.71	0.0861	0.1260	1.44	-1.39
Il1rap1l	5.88	0.57	5.218	0.37	6.52	0.52	0.3189	0.0697	-1.15	1.56
Il6r	6.48	0.21	5.219	0.32	5.71	0.19	0.9958	0.0023	-1.02	-1.71
Il18	2.95	0.28	5.220	0.11	4.52	0.48	0.0002	1.27E-08	1.96	2.97
Impdh1	6.35	0.32	5.221	0.16	5.12	0.39	0.0041	2.23E-07	-1.49	-2.35



Ints8	5.98	0.27	5.222	0.36	6.43	0.26	0.4748	0.0227	-1.11	1.37
Ipo4	6.95	0.23	5.223	0.39	5.77	0.41	0.0362	3.48E-06	-1.24	-2.26
Irak2	5.46	0.24	5.224	0.21	5.58	0.35	0.0003	0.8548	1.71	1.09
Ireb2	6.49	0.32	5.225	0.44	7.46	0.33	0.5310	0.0003	1.26	1.96
Itga5	4.82	0.11	5.226	0.13	5.01	0.41	2.22E-05	0.1913	1.99	1.14
Itgb2	5.02	0.24	5.227	0.37	5.57	0.37	2.34E-05	0.0057	2.33	1.46
Jade1	6.21	0.38	5.228	0.52	6.14	0.16	0.0288	0.6337	-1.67	-1.05
Jrkl	4.64	0.34	5.229	0.5	5.07	0.24	0.6694	0.0713	-1.17	1.35
Kazald1	3.3	0.16	5.230	0.37	3.5	0.16	0.3446	0.2076	-1.33	1.15
Kcna4	6.01	0.31	5.231	0.7	6.98	0.26	0.2262	0.0009	1.27	1.95
Kctd4	4.84	0.46	5.232	0.27	5.47	0.44	0.5481	0.0010	-1.09	1.55
Kdelc2	5.19	0.18	5.233	0.48	5.38	0.43	0.0240	0.8246	-1.56	1.14
Kif4b	4.1	0.2	5.234	0.15	4.56	0.38	0.3695	0.0758	-1.15	1.38
Kif14	2.83	0.14	5.235	0.43	2.97	0.56	0.0018	0.3454	1.71	1.1
Kif24	3.09	0.06	5.236	0.16	3.72	0.32	0.6237	0.0303	-1.03	1.54
Kpna7	3.74	0.31	5.237	0.39	3.91	0.13	0.0441	0.2586	-1.37	1.13
Krt13	5.34	0.5	5.238	0.56	4.88	0.61	0.3990	0.1725	1.33	-1.38
Layn	3.03	0.2	5.239	0.45	3.04	0.46	0.0100	0.6503	1.53	1.01
Lbh	6.53	0.16	5.240	0.38	7.26	0.67	3.14E-05	0.0134	2.54	1.66
Ldlr	7.69	0.2	5.241	0.71	6.76	0.55	0.2318	0.0021	-1.03	-1.9
Limk1	8.57	0.13	5.242	0.44	7.45	0.22	0.0014	4.75E-07	-1.42	-2.17
Lingo1	8.35	0.19	5.243	0.42	6.86	0.31	0.0001	4.42E-09	-1.77	-2.8
Lpl	5.82	0.36	5.244	0.83	6.86	0.32	0.9114	0.0047	1.14	2.05
Lrch2	5.37	0.59	5.245	0.58	6.26	0.49	0.3962	0.0008	1.22	1.86
Lrif1	4.7	0.9	5.246	0.56	5.82	0.54	0.5656	0.0070	1.16	2.17
Lrrce1	4.74	0.32	5.247	0.45	4.93	0.08	0.0616	0.4941	-1.37	1.14
Lrrn4cl	3.64	0.05	5.248	0.55	3.9	0.3	0.0909	0.3005	-1.26	1.2
Lrrtm2	7.98	0.38	5.249	0.38	8.99	0.31	0.0671	2.90E-05	1.27	2.01
Lsm11	5.93	0.19	5.250	0.73	6.14	0.72	0.0025	0.5033	1.98	1.16
Luc7l3	6.18	0.58	5.251	0.35	7.49	0.43	0.1984	0.0005	1.48	2.49
Ly6i	2.74	0.38	5.252	0.36	3.26	0.44	0.7859	0.0229	-1.08	1.43
Lynx1	10.27	0.08	5.253	0.49	8.58	0.48	0.0002	3.30E-07	-2.09	-3.24
Map3k11	6.51	0.1	5.254	0.77	5.07	0.33	0.0161	1.16E-05	-1.57	-2.72
March7	7.65	0.27	5.255	0.12	8.7	0.33	0.0821	2.74E-05	1.37	2.07
Mas1	5.39	0.51	5.256	0.26	4.94	0.23	0.0904	0.6794	1.16	-1.36

Mast3	8.57	0.23	5.257	0.37	6.35	0.57	2.53E-07	4.11E-10	-2.96	-4.67
Mboat2	7.56	0.26	5.258	0.43	7.71	0.38	0.0133	0.7033	-1.43	1.1
Mcpt3	1.97	0.21	5.259	0.44	2.05	0.32	0.0012	0.2385	1.69	1.06
Mcts2	5.03	0.16	5.260	0.15	5.33	0.41	0.1367	0.1208	-1.31	1.24
Med15	7.66	0.15	5.261	0.36	6.4	0.43	0.0163	2.39E-07	-1.33	-2.39
Med25	8.58	0.12	5.262	0.32	6.47	0.74	3.21E-05	9.19E-09	-2.57	-4.32
Mei4	3.75	0.26	5.263	0.37	3.98	0.32	0.0210	0.2316	-1.33	1.18
Mgat4c	4.39	0.36	5.264	0.08	5.31	0.47	0.5295	0.0006	1.17	1.9
Micu3	7.16	0.53	5.265	0.29	8.41	0.53	0.1302	0.0008	1.49	2.37
Midn	8.55	0.4	5.266	0.56	8.09	0.43	0.6130	0.0151	1.25	-1.38
Mier1	5.41	0.46	5.267	0.33	6.23	0.36	0.5032	0.0010	1.04	1.77
Mipol1	5.52	0.37	5.268	0.49	6.4	0.54	0.3357	0.0028	1.19	1.84
Mir21; Vmp1	4.59	0.27	5.269	0.59	5.18	0.48	0.1877	0.0168	-1.61	1.5
Mir150	2.94	0.26	5.270	0.31	2.57	0.4	0.3652	0.0552	1.19	-1.29
Mir181b2	2.49	0.17	5.271	0.06	3.13	0.39	0.4883	0.0039	-1.03	1.56
Mir181c	6.13	0.3	5.272	0.38	6.08	0.3	0.0506	0.8623	-1.7	-1.03
Mir193	2.48	0.26	5.273	0.44	2.51	0.17	0.0004	0.2935	1.59	1.02
Mir212	5.02	0.34	5.274	0.3	4.74	0.47	0.1199	0.3656	1.37	-1.21
Mir299	2.07	0.09	5.275	0.61	2.36	0.12	0.0002	0.2139	1.92	1.22
Mir423; Nsrp1	4.08	0.41	5.276	0.55	4.7	0.31	0.3703	0.1291	1	1.53
Mir3074	4.5	0.3	5.277	0.37	4.49	0.38	0.0081	0.6040	1.6	-1.01
Mir3573	2.13	0.03	5.278	0.77	2.26	0.16	0.0002	0.3951	1.82	1.1
Morc4	4.54	0.26	5.279	0.66	5.68	0.77	0.2042	0.0008	1.13	2.2
Morf4l1	7.59	0.1	5.280	0.46	8.55	0.62	0.1247	9.02E-05	1.09	1.94
Mpp6	6.1	0.51	5.281	0.25	7.29	0.37	0.0773	0.0002	1.48	2.29
Mrpl34	6.76	0.2	5.282	0.27	6.01	0.12	6.41E-07	0.0009	-2.95	-1.69
Mum1l1	3.14	0.1	5.283	0.25	3.86	0.23	0.3567	0.0002	1.04	1.64
Myadm	8.76	0.28	5.284	0.58	7.21	0.71	0.0544	1.13E-05	-1.61	-2.92
Mycs	3.63	0.47	5.285	0.46	3.38	0.15	0.3046	0.2564	1.36	-1.19
Nae1	5.06	0.61	5.286	0.38	6.15	0.65	0.2861	0.0026	1.34	2.12
Nap1l2	7.91	0.18	5.287	0.17	8.17	0.43	0.0291	0.4643	-1.43	1.2
Nap1l5	7.5	0.35	5.288	0.38	8.18	0.06	0.3841	0.0004	1.04	1.6
Nbeal1	5.53	0.39	5.289	0.23	6.56	0.28	0.1502	0.0002	1.34	2.05
Ndst4	5.01	0.55	5.290	0.2	5.03	0.32	0.0161	0.8430	-1.66	1.01
Ndufv3-ps1	7.63	0.25	5.291	0.35	7.37	0.65	0.3897	0.1986	1.3	-1.2
Nedd9	6.08	0.15	5.292	0.47	6.84	0.14	8.96E-08	0.0001	2.64	1.69

Nek10	4.74	0.18	5.293	0.14	4.86	0.38	0.0045	0.9214	-1.43	1.09
Nfix	9.68	0.07	5.294	0.5	8.2	0.46	8.99E-06	1.33E-08	-1.8	-2.8
Nfkbil1	4.69	0.07	5.295	0.53	4.88	0.23	0.0200	0.8633	-1.36	1.14
Nipbl	7.18	0.36	5.296	0.25	8.49	0.24	0.0063	1.60E-06	1.58	2.47
Nkain1	7.74	0.15	5.297	0.41	6.53	0.37	0.0023	3.98E-06	-1.39	-2.32
Noct	7.05	0.3	5.298	0.36	7.74	0.38	1.88E-05	0.0135	2.86	1.62
Nop58	6.28	0.48	5.299	0.15	8.44	0.28	2.23E-07	2.61E-10	2.97	4.5
Npcl	7.84	0.04	5.300	0.38	7.2	0.69	0.5368	0.0542	1.27	-1.56
Nptx2	7.87	0.58	5.301	0.45	9.47	0.65	7.90E-08	7.34E-05	5.55	3.04
Npy2r	4.14	0.17	5.302	0.51	4.31	0.31	0.1352	0.3400	-1.38	1.12
Npy2r	4.11	0.17	5.303	0.5	4.38	0.32	0.1870	0.2330	-1.3	1.21
Nr1d1	10.13	0.21	5.304	0.76	7.27	0.63	1.28E-06	2.50E-09	-3.08	-7.29
Nr1h2	7.7	0.24	5.305	0.25	6.14	0.33	0.0030	3.21E-08	-1.69	-2.95
Nr4a1	8.79	0.47	5.306	0.87	9.15	0.78	0.0402	0.8601	2.1	1.28
Nts	5.52	0.75	5.307	2.58	9.35	0.71	0.0146	2.26E-05	4.3	14.28
Oas1a	5.6	0.5	5.308	0.37	5.36	0.24	0.0563	0.2916	1.42	-1.18
Obp2b	3.69	0.45	5.309	0.26	4.29	0.35	0.0091	0.0234	-1.65	1.52
Ogdh	10.32	0.17	5.310	0.36	8.49	0.44	2.96E-05	2.05E-08	-2.13	-3.57
Olr4	3.08	0.29	5.311	0.17	3.13	0.27	0.0067	0.8969	1.62	1.04
Olr14	2.36	0.09	5.312	0.56	2.33	0.36	0.0056	0.8276	1.56	-1.02
Olr53	2.58	0.32	5.313	0.52	2.36	0.36	0.0307	0.9409	1.57	-1.16
Olr82	2.94	0.13	5.314	0.38	2.68	0.32	0.0265	0.3219	1.58	-1.2
Olr85	2.74	0.21	5.315	0.4	2.91	0.26	0.0002	0.7295	2.01	1.13
Olr87	2.83	0.17	5.316	0.13	3.17	0.31	0.1061	0.0247	-1.25	1.26
Olr114	2.12	0.11	5.317	0.51	2.19	0.3	0.0006	0.4113	1.63	1.05
Olr165	2.16	0.11	5.318	0.58	2.34	0.28	0.0021	0.5752	2.04	1.13
Olr233	2.18	0.14	5.319	0.63	2.25	0.14	0.0007	0.5824	1.67	1.05
Olr288	3.96	0.25	5.320	0.24	3.73	0.48	0.0649	0.8614	1.38	-1.17
Olr303	2.08	0.1	5.321	0.39	2.33	0.13	0.0006	0.1141	1.79	1.19
Olr346	2.37	0.07	5.322	0.38	2.43	0.21	0.0001	0.2932	1.57	1.04
Olr382	2.47	0.01	5.323	0.41	2.7	0.3	7.44E-05	0.1023	1.94	1.18
Olr429	3.29	0.3	5.324	0.36	3.51	0.29	0.0011	0.1596	1.8	1.17
Olr470	2.72	0.21	5.325	1.13	2.94	0.24	0.0093	0.7076	1.84	1.16
Olr484	2.27	0.2	5.326	0.83	2.38	0.19	0.0017	0.3504	1.78	1.08
Olr485	2.21	0.16	5.327	0.33	2.58	0.14	0.0003	0.1729	1.96	1.29

Olr546	2.77	0.34	5.328	0.57	2.45	0.16	0.0176	0.4155	1.44	-1.25
Olr598	2.68	0.12	5.329	0.48	2.98	0.36	0.0009	0.1353	1.98	1.24
Olr606	2.31	0.12	5.330	0.77	2.49	0.33	0.0028	0.6854	1.72	1.13
Olr687	3.16	0.16	5.331	0.33	3.28	0.17	0.0005	0.9887	1.93	1.09
Olr777	3.19	0.35	5.332	0.23	3.8	0.67	0.6175	0.0078	-1.17	1.53
Olr783	2.2	0.12	5.333	0.53	2.26	0.34	0.0008	0.7267	1.86	1.04
Olr796	2.45	0.11	5.334	0.62	2.47	0.22	0.0005	0.5735	1.84	1.02
Olr806	2.49	0.19	5.335	0.44	2.34	0.27	0.0346	0.4285	1.37	-1.11
Olr860	3.39	0.21	5.336	0.28	3.93	0.27	0.4765	0.0101	-1.21	1.45
Olr867	1.92	0.09	5.337	0.71	2.17	0.22	0.0002	0.2736	1.95	1.19
Olr892	2.05	0.14	5.338	0.18	2.07	0.21	0.0006	0.7410	1.62	1.02
Olr954	2.66	0.3	5.339	0.34	2.76	0.19	0.0043	0.6805	1.66	1.07
Olr1060	1.92	0.18	5.340	0.65	2.21	0.14	0.0004	0.2534	1.87	1.23
Olr1202	2.3	0.05	5.341	0.18	2.57	0.34	4.91E-05	0.0674	1.88	1.2
Olr1203	2.83	0.42	5.342	0.16	2.52	0.51	0.1787	0.5241	1.27	-1.24
Olr1214	3.74	0.28	5.343	0.96	4.8	0.71	0.9613	0.0172	1.22	2.09
Olr1226	2.47	0.16	5.344	0.6	2.47	0.41	0.0031	0.5065	1.62	-1
Olr1231	2.26	0.16	5.345	0.56	2.05	0.24	0.0664	0.4005	1.34	-1.16
Olr1243	2.09	0.14	5.346	0.41	2.33	0.18	0.0004	0.1289	1.77	1.18
Olr1257	2.12	0.08	5.347	0.19	3.01	0.37	0.5570	0.0017	1.13	1.85
Olr1313	4.29	0.24	5.348	0.41	4.5	0.82	0.0184	0.6600	-1.83	1.15
Olr1325	3.01	0.21	5.349	0.79	3.18	0.24	0.0010	0.4563	1.94	1.12
Olr1382	2.25	0.15	5.350	0.83	2.36	0.29	0.0012	0.7380	2	1.08
Olr1407	2.38	0.14	5.351	0.59	2.42	0.2	0.0006	0.8132	1.62	1.03
Olr1462	3.89	0.25	5.352	0.37	4.33	0.32	0.0465	0.0047	-1.23	1.36
Olr1468	3.72	0.17	5.353	0.27	3.61	0.25	0.0004	0.5016	1.62	-1.09
Olr1488	3.89	0.48	5.354	0.15	4.21	0.17	0.0278	0.1740	-1.41	1.25
Olr1514	3.33	0.33	5.355	0.62	3.05	0.57	0.0523	0.8279	1.6	-1.21
Olr1601	2.92	0.17	5.356	0.46	3.7	0.28	0.4876	0.0055	1.13	1.72
Olr1707	2.65	0.18	5.357	0.41	2.71	0.21	0.0026	0.3274	1.57	1.04
Olr1736	3.56	0.2	5.358	0.52	4.42	0.73	0.6933	0.0053	1.13	1.82
Orc4	6.71	0.7	5.359	0.23	8.46	0.59	0.0155	5.54E-06	2.08	3.37
Ostc	5.24	0.3	5.360	0.65	6.02	0.39	0.4110	0.0011	1.02	1.72
Ostn	3.33	0.08	5.361	0.24	3.3	0.13	1.49E-05	0.7028	1.7	-1.02
Pak6	7.57	0.12	5.362	0.1	6.58	0.42	0.1389	0.0002	-1.21	-1.99
Paqr6	7.04	0.21	5.363	0.25	5.71	0.54	0.0245	5.07E-07	-1.35	-2.52
Pbdc1	6.22	0.26	5.364	0.66	7.34	0.2	0.2143	1.79E-05	1.34	2.17
Pc	8.16	0.19	5.365	0.46	6.36	0.51	7.26E-05	3.83E-08	-2.28	-3.47

Pcdh19	7.18	0.17	5.366	0.35	6.72	0.29	2.20E-06	0.0036	-2.13	-1.37
Pcdhb9	5.23	0.41	5.367	0.5	5.54	0.78	0.0091	0.5369	-1.75	1.25
Pdcl	6.6	0.2	5.368	0.48	6.79	0.48	0.0124	0.6731	-1.73	1.14
Pde1c	4.26	0.34	5.369	0.41	4.92	0.45	0.8250	0.0255	-1.13	1.58
Per1	8.28	0.17	5.370	0.44	6.77	0.7	0.0175	7.65E-06	-1.74	-2.84
Pfkfb2	5.45	0.27	5.371	0.23	5.43	0.12	0.0038	0.8413	-1.53	-1.01
Pfkip	10.37	0.06	5.372	0.19	9.83	0.36	0.9202	0.0135	1.05	-1.45
Phip	6.78	0.36	5.373	0.51	7.81	0.2	0.5929	0.0003	1.14	2.04
Pik3r3	6.99	0.41	5.374	0.55	7.5	0.26	0.1843	0.1879	-1.14	1.43
Plcx3	6.05	0.45	5.375	0.82	7.49	0.53	0.1940	0.0002	1.76	2.71
Plec	7.24	0.14	5.376	0.3	6.49	0.55	0.3173	0.0013	-1.1	-1.69
Plek2	3.78	0.33	5.377	0.49	4.67	0.43	0.3230	0.0018	1.14	1.86
Plekha2	5.39	0.21	5.378	0.59	4.55	0.4	0.5136	0.0062	-1.08	-1.79
Plekhb1	9.95	0.4	5.379	0.2	9.94	0.28	0.1155	0.6126	1.5	-1.01
Plk3	6.07	0.26	5.380	0.38	6.28	0.28	0.0012	0.4881	2.13	1.16
Pllp	8.11	0.08	5.381	0.28	7.14	0.49	0.2016	5.28E-05	-1.22	-1.97
Plppr1	7.21	0.43	5.382	1.03	7.33	0.36	0.1125	0.6408	-1.49	1.08
Pola1	4.62	0.37	5.383	0.25	5.24	0.39	0.9100	0.0044	-1.05	1.53
Porcn	7.42	0.09	5.384	0.24	5.84	0.19	8.20E-05	2.75E-09	-1.82	-2.99
Pou6f1	7.58	0.03	5.385	0.53	5.77	0.4	6.42E-06	8.76E-09	-2.15	-3.51
Ppard	7.29	0.07	5.386	0.42	6.62	0.31	0.7274	0.0006	-1.01	-1.58
Ppp2r1a	10.66	0.15	5.387	0.45	9.22	0.56	0.0336	1.75E-05	-1.4	-2.72
Ppp4r3b	5.94	0.41	5.388	0.38	7.56	0.35	0.0059	1.59E-06	1.86	3.09
Ppwd1	5.09	0.48	5.389	0.32	6.4	0.59	0.1801	9.32E-05	1.54	2.48
Pramef8	4.8	0.2	5.390	0.2	4.93	0.14	0.0023	0.7823	1.65	1.1
Pramel7	3.46	0.21	5.391	0.58	3.34	0.34	0.0256	0.7973	1.54	-1.09
Prim1	5.8	0.47	5.392	0.71	6.02	0.74	0.2541	0.2713	-1.38	1.16
Prkar2b	7.33	0.33	5.393	0.81	8.05	0.46	0.9496	0.0123	-1	1.65
Prkcg	9.78	0.14	5.394	0.43	8.1	0.36	1.21E-05	3.92E-09	-1.88	-3.22
Prkcsh	8.74	0.15	5.395	0.35	7.7	0.42	0.0870	0.0003	-1.25	-2.04
Pros1	4.9	0.43	5.396	0.53	5.61	0.42	0.3185	0.1193	1.02	1.63
Prpf39	6.15	0.66	5.397	0.26	8.32	0.44	0.0141	2.28E-06	2.15	4.51
Prpf40a	6.8	0.39	5.398	0.57	8.03	0.55	0.0596	0.0001	1.46	2.34
Prr3	7.17	0.08	5.399	0.32	6.45	0.54	0.7638	0.0065	-1.03	-1.66
Prr15	4.13	0.29	5.400	0.44	3.97	0.18	0.2959	0.2419	1.39	-1.11
Psrc1	5.5	0.22	5.401	0.31	4.61	0.36	0.1653	0.0003	-1.09	-1.85

Psx1	4.37	0.26	5.402	0.36	4.59	0.29	0.0753	0.4883	-1.45	1.17
Ptchd2	6.66	0.17	5.403	0.33	5.54	0.34	0.2681	9.76E-05	-1.15	-2.16
Ptges3l1	3.38	0.16	5.404	0.31	3.82	0.31	0.2661	0.0237	-1.16	1.36
Pts	4.3	0.13	5.405	0.1	4.85	0.37	0.7086	0.0251	-1.04	1.46
Ptx3	3.81	0.36	5.406	0.49	6.47	0.56	7.21E-13	2.84E-10	11.38	6.32
Pus1	5.2	0.19	5.407	0.33	4.89	0.13	0.0471	0.0924	1.24	-1.24
Pus10	5.81	0.19	5.408	0.27	6.28	0.29	0.2497	0.0194	-1.28	1.38
PVR	4.84	0.12	5.409	0.31	5.91	0.23	1.54E-09	3.90E-06	3.43	2.1
Pvrl1	8.82	0.07	5.410	0.44	7.79	0.21	0.0373	1.23E-05	-1.35	-2.04
Rasa2	6.1	0.41	5.411	0.31	7.08	0.38	0.5227	0.0022	1.27	1.97
Rasl11a	4.61	0.27	5.412	0.48	4.76	0.2	0.0009	0.4477	1.88	1.11
Rassf7	5.15	0.24	5.413	0.38	5.2	0.26	0.0668	0.7574	-1.45	1.04
Rbbp8	5.43	0.43	5.414	0.48	6.26	0.39	0.2008	0.0012	1.1	1.77
Rbm34	6.41	0.47	5.415	0.2	7.15	0.55	0.9217	0.0106	1.04	1.67
Rbmx11	5.24	0.56	5.416	0.44	5.64	0.35	0.3913	0.0810	-1.21	1.32
Rc3h1	4.56	0.5	5.417	0.55	5.4	0.35	0.5991	0.0379	-1.06	1.79
Repin1	5.65	0.21	5.418	0.13	4.38	0.51	0.1165	1.74E-05	-1.24	-2.41
Rgs16	6.73	0.27	5.419	0.36	8.03	0.27	8.51E-09	7.21E-07	3.92	2.46
Rimbp2	7.88	0.07	5.420	0.42	7.24	0.37	0.6758	0.0126	-1.02	-1.56
Rnase4	3.58	0.31	5.421	0.22	3.94	0.64	0.2227	0.1589	-1.33	1.29
Rnf113a1	4.35	0.08	5.422	0.28	4.6	0.58	0.0367	0.8368	-1.46	1.19
Rnf128	4.63	0.4	5.423	0.21	5.28	0.55	0.4908	0.0342	-1.05	1.57
Rnf223	5.19	0.27	5.424	0.26	5.21	0.48	0.0156	0.8495	-1.48	1.01
Rock1	5.93	0.76	5.425	0.28	7.92	0.46	0.0091	2.58E-06	1.99	3.97
Rpgrip11	6	0.44	5.426	0.47	6.13	0.48	0.0181	0.8833	-1.52	1.09
Rpl26	3.05	0.27	5.427	0.36	3.3	0.49	0.2150	0.4108	-1.3	1.19
Rps16	5.64	0.18	5.428	0.38	4.94	0.66	0.3517	0.0496	1.09	-1.63
Rpusd2	5.49	0.21	5.429	0.25	4.45	0.39	0.1035	3.10E-05	-1.27	-2.06
Rsb1	5.86	0.34	5.430	0.2	7.03	0.37	0.0398	1.22E-05	1.44	2.24
Rslcan18	7	0.42	5.431	0.33	7.33	0.4	0.0153	0.0877	-1.5	1.26
RT1-M6-2	4.75	0.51	5.432	0.54	5.05	0.68	0.0015	0.8284	2.96	1.23
Rtkn2	4.76	0.07	5.433	0.18	4.08	0.49	0.3961	0.0021	-1.06	-1.6
Rundc1	7.6	0.09	5.434	0.5	6.53	0.71	0.1615	0.0010	-1.1	-2.11
Rwdd3	4.64	0.27	5.435	0.52	4.47	0.38	0.0009	0.0814	-1.92	-1.12
Satb2	8.43	0.12	5.436	0.52	7	0.4	0.0007	3.84E-07	-1.76	-2.7

Scap	9.34	0.27	5.437	0.31	7.73	0.48	0.0005	9.27E-08	-1.74	-3.04
Scaper	7.14	0.43	5.438	0.65	7.82	0.41	0.0398	0.2028	-1.23	1.6
Scarna3	3.04	0.07	5.439	0.66	3.59	0.43	2.64E-06	0.0326	3.72	1.46
Sdk2	7.13	0.17	5.440	0.44	6.17	0.54	0.2941	0.0006	-1.04	-1.95
Sdsl	4.43	0.41	5.441	0.41	4.58	0.41	0.0792	0.7031	-1.44	1.11
Sema5b	6.37	0.16	5.442	0.5	5.17	0.36	0.0009	1.80E-06	-1.42	-2.3
Senp6	7.35	0.59	5.443	0.32	8.4	0.31	0.1812	0.0010	1.35	2.07
Serpinb6	4.95	0.32	5.444	0.08	6.14	0.47	0.1594	3.41E-05	1.32	2.29
Serpine1	4.27	0.25	5.445	0.44	6.47	0.81	5.08E-09	7.80E-07	8.59	4.59
Sertad1	4.91	0.37	5.446	0.18	5.03	0.25	0.0003	0.1542	1.72	1.09
Sf3a2	7.24	0.27	5.447	0.37	6.33	0.31	3.15E-07	0.0003	-2.86	-1.87
Sgsm1	7.76	0.17	5.448	0.55	6.81	0.43	0.0368	0.0002	-1.18	-1.93
Shkbp1	5.76	0.28	5.449	0.4	5.15	0.34	0.6120	0.0040	1.08	-1.53
Shroom3	4.66	0.26	5.450	0.31	4.13	0.58	0.3313	0.0196	1.3	-1.44
Sirt1	6.15	0.45	5.451	0.23	6.98	0.4	0.8878	0.0059	1.05	1.78
Sirt2	10.35	0.17	5.452	0.23	10.17	0.33	0.2870	0.2748	1.34	-1.13
Slamf1	3.58	0.15	5.453	0.17	3.84	0.42	0.0008	0.2017	1.83	1.2
Slc2a1	9.63	0.05	5.454	0.41	8.9	0.56	0.4491	0.0053	-1.06	-1.66
Slc2a8	7.73	0.32	5.455	0.32	6.48	0.48	0.0053	4.05E-06	-1.54	-2.39
Slc5a7	4.37	0.57	5.456	0.79	5.86	1.13	0.8867	0.0079	1.23	2.81
Slc6a18	3.36	0.14	5.457	0.24	3.69	0.18	0.0192	0.0733	-1.3	1.26
Slc7a5	8.67	0.15	5.458	0.67	7.6	0.59	0.0922	0.0004	-1.26	-2.1
Slc7a13	2.32	0.13	5.459	0.42	2.41	0.13	0.0010	0.8497	1.77	1.07
Slc11a1	4.39	0.07	5.460	0.32	4.08	0.39	0.0136	0.1502	1.44	-1.24
Slc18a2	3.42	0.13	5.461	0.32	3.74	0.24	0.2655	0.2750	-1.23	1.25
Slc24a2	10.24	0.16	5.462	0.47	8.97	0.47	0.0086	1.84E-05	-1.32	-2.4
Slc25a2	3.98	0.37	5.463	0.49	4.28	0.45	0.1813	0.0337	-1.28	1.24
Slc25a12	9.89	0.13	5.464	0.58	8.49	0.64	0.0407	5.06E-05	-1.35	-2.63
Slc25a45	3.68	0.38	5.465	0.25	3.76	0.08	0.0131	0.6918	-1.42	1.06
Slc27a4	7.44	0.11	5.466	0.13	6.18	0.36	0.0440	7.45E-08	-1.25	-2.4
Slc29a2	5.84	0.22	5.467	0.45	4.02	0.49	0.0007	1.40E-06	-2.07	-3.52
Slc43a1	3.57	0.24	5.468	0.59	2.89	0.43	0.5389	0.1490	1	-1.6
Slc45a2	3.7	0.29	5.469	0.35	3.84	0.38	0.0157	0.6330	-1.53	1.11
Slx4ip	4.41	0.21	5.470	0.4	4.64	0.17	0.0373	0.1380	-1.36	1.17
Smagp	4.26	0.09	5.471	0.41	4.53	0.32	0.0014	0.1144	1.87	1.21

Smarca1	5.53	0.28	5.472	0.68	6.33	0.51	0.5961	0.0084	1.03	1.74
Smim17	5.92	0.17	5.473	0.28	5.76	0.44	0.0008	0.1364	-1.71	-1.12
Snpc5	7.96	0.14	5.474	0.26	7.95	0.36	0.0022	0.5990	-1.51	-1.01
Snora58	3.93	0.11	5.475	1.04	4.6	0.61	0.0023	0.2476	2.5	1.58
Snx8	6.32	0.05	5.476	0.41	5.51	0.38	0.1464	0.0005	-1.12	-1.75
Snx24	5.45	0.45	5.477	0.47	6.14	0.32	0.9695	0.0068	-1.02	1.61
Sowahb	5.62	0.34	5.478	0.52	5.42	0.46	0.0490	0.5753	1.72	-1.14
Spag6	4.72	0.17	5.479	0.23	5.57	0.47	0.7954	0.0029	1.12	1.8
Spata5	4.46	0.29	5.480	0.28	5.48	0.36	0.2672	0.0005	1.2	2.04
Spp12b	6.84	0.15	5.481	0.54	6.12	0.32	0.2755	0.0005	1.02	-1.65
Sprr1a	4.71	0.22	5.482	0.51	6.03	1.2	3.44E-06	0.0016	4.72	2.5
Srm	8.2	0.12	5.483	0.13	7.75	0.3	0.2050	0.0501	1.22	-1.36
Ssb	5.03	0.35	5.484	0.43	6.12	0.66	0.3296	0.0002	1.19	2.12
Ssbp4	9.07	0.06	5.485	0.15	8.28	0.23	0.3415	0.0001	-1.1	-1.72
St8sia4	5.02	0.32	5.486	0.29	5.42	0.43	0.1830	0.0980	-1.16	1.32
St8sia5	8.5	0.16	5.487	0.21	7.44	0.5	0.0210	1.30E-05	-1.3	-2.09
Stag1	5.9	0.44	5.488	0.21	6.92	0.44	0.3618	0.0007	1.26	2.02
Stard3	7.41	0.16	5.489	0.26	5.89	0.73	0.0718	2.15E-05	-1.39	-2.86
Stat2	6.72	0.19	5.490	0.35	5.88	0.41	0.3074	0.0009	-1.13	-1.78
Strip2	6.83	0.28	5.491	0.95	7.59	0.57	0.3185	0.2999	-1.3	1.7
Sult1d1	3.94	0.68	5.492	0.2	5.26	0.75	0.3815	0.0058	1.6	2.49
Suv420h1	6.93	0.32	5.493	0.42	7.65	0.41	0.5801	0.0068	1.06	1.65
Swt1	5.02	0.42	5.494	0.17	6.33	0.59	0.0172	1.69E-05	1.64	2.48
Syt10	6.85	0.2	5.495	0.95	8.28	0.37	0.0576	0.0001	1.41	2.68
Tatdn1	4.95	0.64	5.496	0.33	6.09	0.41	0.9254	0.0016	1.21	2.2
Tbc1d20	7.26	0.15	5.497	0.34	6.64	0.58	0.4535	0.0014	-1	-1.53
Tc2n	4.27	0.39	5.498	0.63	5.16	1.04	0.8563	0.0095	1.04	1.85
Tcea1	6.75	0.48	5.499	0.32	8.05	0.42	0.0009	8.06E-07	1.54	2.46
Tceal8	5.14	0.66	5.500	0.88	6.38	0.47	0.4426	0.0012	1.57	2.37
Tceb1	4.68	0.29	5.501	0.45	5.49	0.57	0.7692	0.0116	-1	1.75
Tet3	6.3	0.14	5.502	0.47	6.24	0.57	0.0631	0.8445	1.6	-1.05
Tfdp2	5.98	0.44	5.503	0.38	6.21	0.41	0.0566	0.3426	-1.32	1.17
Tgfb1	6.17	0.35	5.504	0.2	6.55	0.32	4.47E-06	0.0061	2.06	1.3
Thoc7	5.37	0.18	5.505	0.53	6.72	0.36	0.0032	5.78E-06	1.57	2.55
Thrsp	8.63	0.22	5.506	0.24	8.05	0.23	0.4845	0.0376	1.07	-1.5
Timm10b	4.48	0.55	5.507	0.16	5.21	0.43	0.1863	0.0179	-1.21	1.66
Tinagl1	6.17	0.08	5.508	0.59	5.47	0.47	0.7804	0.0221	1.25	-1.63



Tlr11	2.71	0.26	5.509	0.61	2.56	0.16	0.0828	0.4024	1.53	-1.11
Tmem2	5.79	0.02	5.510	0.43	6.44	0.33	4.27E-06	0.0017	2.38	1.56
Tmem80	5.97	0.19	5.511	0.32	4.8	0.5	0.0138	2.12E-05	-1.42	-2.25
Tmem104	6.31	0.14	5.512	0.41	5.38	0.71	0.2873	0.0029	-1.08	-1.9
Tmem126b	5.27	0.13	5.513	0.7	5.13	0.32	0.0023	0.6749	-1.68	-1.1
Tmem198	7.77	0.26	5.514	0.29	6.99	0.2	0.7187	0.0018	-1.12	-1.71
Tmem251	4.78	0.11	5.515	0.45	5.84	0.38	0.1541	1.32E-05	1.21	2.08
Tmem259	8.81	0.12	5.516	0.35	7.43	0.35	0.0003	5.14E-08	-1.64	-2.61
Tnfrsf10b	3.34	0.12	5.517	0.2	3.43	0.37	0.0004	0.3690	1.71	1.06
Tnfrsf12a	5.26	0.3	5.518	0.09	6.49	0.29	1.05E-10	1.96E-07	3.86	2.36
Tomm40	9.02	0.06	5.519	0.19	7.97	0.33	0.2132	0.0003	-1.21	-2.07
Tomm70a	8.34	0.27	5.520	0.88	9.8	0.32	0.0265	2.47E-05	1.5	2.76
Topors	5.51	0.12	5.521	0.26	5.84	0.5	0.3694	0.1011	-1.2	1.26
Tppp	10.56	0.15	5.522	0.74	9.48	0.6	0.3575	0.0031	1.06	-2.12
Trim34	3.95	0.29	5.523	0.32	3.67	0.56	0.1324	0.5750	1.31	-1.22
Trim54	6.44	0.27	5.524	0.6	5.29	0.6	0.4848	0.0008	-1.2	-2.22
Trmt2a	5.92	0.26	5.525	0.28	5.37	0.64	0.6760	0.0235	1.07	-1.46
Trnt1	5.32	0.27	5.526	0.69	6.69	0.37	0.0675	9.75E-05	1.26	2.57
Trpm7	5.7	0.45	5.527	0.09	6.79	0.23	0.3129	0.0006	1.38	2.13
Trpt1	4.97	0.29	5.528	0.18	4.03	0.68	0.1104	0.0004	-1.2	-1.92
Ttyh3	10.12	0.06	5.529	0.62	7.71	0.72	2.45E-06	4.11E-09	-2.68	-5.3
U2surp	7.61	0.49	5.530	0.55	8.53	0.36	0.2897	0.0020	1.26	1.9
Uba6	7.1	0.29	5.531	0.48	8.12	0.42	0.2501	7.51E-05	1.31	2.04
Ube2d2	6.97	0.42	5.532	0.37	7.8	0.28	0.6719	0.0049	1.08	1.77
Ubl7	10.83	0.21	5.533	0.31	8.81	0.47	0.0002	9.14E-08	-2.18	-4.06
Ubxn2b	6.94	0.52	5.534	0.36	7.21	0.23	0.2025	0.4817	-1.35	1.21
Ugt2b17	2.08	0.18	5.535	0.64	2.34	0.39	0.0002	0.1609	1.91	1.2
Unc5a	8.89	0.17	5.536	0.52	7.17	0.19	2.23E-07	3.00E-10	-2.05	-3.29
Unc13d	4.06	0.25	5.537	0.24	4.26	0.4	0.0291	0.4264	-1.47	1.15
Usp37	6.11	0.38	5.538	0.42	6.82	0.24	0.7706	0.0024	-1.03	1.63
Vcsa1	2.31	0.05	5.539	0.55	3.12	0.47	0.2937	0.0028	1.16	1.75
Vegp2	3.18	0.28	5.540	0.38	2.67	0.6	0.3499	0.0508	1.25	-1.43
Vom1r7	2	0.16	5.541	0.07	2.84	0.4	0.4502	0.0002	1.1	1.79
Vom1r14	2.14	0.34	5.542	0.34	2.38	0.24	0.0057	0.6038	1.81	1.17
Vom1r19	3.01	0.18	5.543	0.26	3.65	0.4	0.7815	0.0148	-1.1	1.55

Vom1r37	2.94	0.2	5.544	0.51	2.97	0.26	0.0012	0.5077	1.6	1.02
Vom1r42	2.13	0.15	5.545	0.52	2.14	0.19	0.0405	0.8609	1.69	1.01
Vom1r54	3.03	0.28	5.546	1.05	3	0.4	0.0110	0.9176	1.64	-1.02
Vom1r67	2.74	0.11	5.547	0.47	2.62	0.33	0.0026	0.3978	1.72	-1.09
Vom1r101	2.23	0.1	5.548	0.59	2.52	0.21	2.07E-05	0.1286	1.92	1.22
Vom2r6	2.3	0.1	5.549	0.45	2.35	0.38	0.0016	0.3177	1.66	1.04
Vom2r61	1.98	0.2	5.550	0.52	2.2	0.14	3.25E-05	0.1487	1.98	1.16
Vom2r76	2.44	0.29	5.551	0.49	2.51	0.31	0.0017	0.7180	1.64	1.05
Vps16	6.96	0.18	5.552	0.27	5.47	0.56	0.0053	4.81E-06	-1.68	-2.79
Vps52	7.42	0.25	5.553	0.26	6.11	0.38	0.0040	2.28E-06	-1.42	-2.49
Wdr46	7.2	0.34	5.554	0.52	6.23	0.5	0.3599	0.0012	-1.01	-1.96
Wnt7b	6.74	0.14	5.555	0.24	6.08	0.61	0.9056	0.0093	-1.01	-1.58
Xpa	4.69	0.25	5.556	0.16	5.05	0.24	0.1448	0.0975	-1.2	1.28
Xrcc2	4.1	0.21	5.557	0.31	4.4	0.21	0.0353	0.1078	-1.25	1.23
Xrn1	6.41	0.38	5.558	0.13	7.17	0.21	0.6530	0.0049	1.05	1.69
Zbtb26	4.65	0.23	5.559	0.55	5.38	0.19	0.6518	0.0087	-1.1	1.66
Zfand2b	6.01	0.16	5.560	0.3	5.31	0.27	0.3799	0.0004	-1.04	-1.63
Zfand4	4.13	0.37	5.561	0.2	4.91	0.15	0.9962	0.0023	1.09	1.72
Zfp62	5.68	0.55	5.562	0.34	7.38	0.35	0.0847	4.33E-05	1.61	3.23
Zfp110	5.65	0.26	5.563	0.17	5.3	0.63	0.5973	0.0299	1.21	-1.28
Zfp280c	5.92	0.55	5.564	0.15	7.02	0.55	0.1417	7.01E-05	1.31	2.15
Zfp280d	6.3	0.49	5.565	0.41	7.57	0.43	0.0507	3.13E-05	1.43	2.41
Zfp420	4.12	0.46	5.566	0.43	4.33	0.47	0.0401	0.9525	-1.39	1.16
Zfp458	3.5	0.32	5.567	0.26	4.43	0.57	0.8673	0.0084	1.1	1.9
Zfp597	6.35	0.15	5.568	0.48	6.75	0.28	0.4887	0.1788	-1.18	1.32
Zfp605	5.47	0.39	5.569	0.26	6.46	0.32	0.1848	0.0002	1.26	1.99
Zfp622	4.71	0.4	5.570	0.27	4.59	0.38	0.1285	0.1526	1.44	-1.09
Zfp638	6.83	0.37	5.571	0.57	7.95	0.4	0.0702	0.0002	1.33	2.18
Zfp780b	3.48	0.39	5.572	0.56	5.16	0.56	0.0042	6.66E-06	2.01	3.2
Zfp867	4.32	0.33	5.573	0.16	4.37	0.48	0.0021	0.8077	-1.57	1.03
Zfp945	2.72	0.73	5.574	0.32	4.14	0.98	0.2165	0.0004	1.43	2.67
Zic2	6.71	0.46	5.575	0.72	6.09	0.82	1.11E-05	0.0044	-3.26	-1.54
Zmiz1	8.56	0.06	5.576	0.55	7.98	0.94	0.6234	0.0647	1.34	-1.5
Zmynd8	8.17	0.23	5.577	0.16	7.36	0.53	0.4066	0.0029	-1.1	-1.75
Znf354b	4.15	0.42	5.578	0.37	4.22	0.4	0.0768	0.2654	-1.48	1.05
Znf768	5	0.08	5.579	0.16	4.37	0.21	0.8438	0.0002	1.05	-1.55

