(1) Title: Assessment of CSF biomarkers and microRNA-mediated disease mechanisms in SMA

Running head: CSF biomarker and microRNA assessment in SMA

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Abstract

Objective: Cerebral spinal fluid (CSF) is a promising biospecimen for the detection of central nervous system (CNS) biomarkers to monitor therapeutic efficacy at the cellular level in neurological diseases. Spinal muscular atrophy (SMA) patients receiving intrathecal antisense oligonucleotide (nusinersen) therapy tend to show improved motor function, but the treatment effect on cellular function remains unknown. The objective of this study was to assess the potential of extracellular RNAs and microRNAs in SMA patient CSF as indicators of neuron and glial health following nusinersen treatment.

Methods: CSF samples from SMA Type 1-3 patients were screened using quantitative RT-PCR to assess expression of extracellular RNAs associated with inflammation and cellular stress, and microRNAs previously implicated in SMA pathogenesis. We also used mRNA sequencing and multi-electrode array approaches to assess the transcriptional and functional effects of astrocyte-associated miR-146a on healthy and SMA induced pluripotent stem cell (iPSC)-derived motor neurons.

Results: Extracellular RNA analysis is suggestive of ongoing cellular stress, even in nusinersen treated samples. microRNAs previously associated with SMA pathology tended to show improvement in expression levels in nusinersen treated samples, with the exception of the astrocyte-secreted miR-146a. miR-146a treated iPSC-derived motor neurons showed a downregulation of extracellular matrix genes found in the synaptic perineuronal net and decreased spontaneous activity.

Interpretation: Extracellular RNAs and microRNAs can be detected in SMA patient CSF samples, potentially serving as useful biomarkers to monitor cellular health during nusinersen treatment. Astrocyte health and response to nusinersen are important aspects to address in SMA pathogenesis and treatment strategies.

Introduction

Spinal muscular atrophy (SMA) is the leading genetic cause of pediatric mortality (1) and is caused by the homozygous disruption of the *Survival of Motor Neuron-1* (*SMN1*) gene. *SMN1* is responsible for generating full length SMN protein, which has an established global role in small nuclear ribonucleoprotein (RNP) assembly and pre-mRNA splicing (2), and is particularly important for motor neuron function (3, 4). Reduced SMN leads to selective lower spinal motor neuron degeneration and subsequent loss of skeletal muscle innervation leading to paralysis, respiratory failure, and premature death. A human specific *SMN1* paralog, *SMN2*, can partially produce full length SMN protein and modify SMA disease severity (5, 6), but a single nucleotide change within the splicing enhancer region of *SMN2* exon 7 (c.840C>T) causes aberrant exon 7 splicing, generating an unstable, non-functional SMN protein which is targeted for degradation (7, 8).

Efforts to develop antisense oligonucleotide technology to facilitate *SMN2* splicing correction and increase full length SMN protein levels led to the first FDA approved drug, nusinersen, for SMA (9). Nusinersen is delivered intrathecally into the CNS, where it targets the *SMN2* intronic splicing silencer, blocking the binding of heterogenous nuclear RNP A1 that represses exon 7 inclusion (10). Target specificity, minimal toxicity, and long half-life properties have been demonstrated for nusinersen and remarkable improvements in motor milestone achievements are observed in patients treated pre-symptomatically (11, 12). However, improvements at the cellular level post treatment is not fully understood. CSF biomarker detection that can reliably track improvements in CNS cellular health and correlate with motor functioning recovery has high clinical value. In this regard, studies have begun to assess biomarkers in SMA CSF samples after nusinersen treatment, such as neurofilament light chain (13, 14) and synaptic-associated proteins (15), however, the reliability of these markers is still in question. In other neurodegenerative diseases, microRNAs are promising biomarkers detectable in CSF samples (16-18), but they have yet to be explored in SMA patient CSF samples. Further work is also needed to fully define SMA cell autonomous and non-cell autonomous disease mechanisms, which will ultimately impact biomarker discovery efforts.

In this study, we screened SMA patient CSF samples before and after multiple doses of nusinersen for extracellular RNAs and microRNAs to facilitate biomarker discovery. Overall, we observe that cellular stress RNAs are still present in the CSF even after treatment administration. Although we observe an overall post treatment improvement in microRNA expression levels previously associated with SMA disease pathology, the astrocyte-secreted miR-146a, which we previously show to be toxic to SMA motor neurons (19), remains elevated in SMA patient CSF. We further demonstrate miR-146a alters perineuronal net extracellular matrix gene expression in iPSC-derived motor neurons, which may affect synaptic functioning. Taken together, these data suggest that extracellular RNAs and microRNAs detected in patient CSF may be valuable for tracking cellular health in response to nusinersen treatment. Additional studies focused on astrocyte-mediated disease mechanisms, nusinersen uptake and cellular recovery will be important to ensure long term efficacy of therapies for SMA.

Methods

Human samples

CSF samples were obtained at Children's Wisconsin with informed consent during standard clinical care for the administration of SMA-related nusinersen ASO therapy (IRB 1080061). A total of 35 CSF samples were used in this study from SMA Type 1 (4 patients), Type 2 (5 patients) and Type 3 (3 patients). Deidentified SMA patient information related to pre- and post-nusinersen treated CSF biospecimens analyzed in this study and motor functioning scores, are detailed in Table 1. Before each dose, the patients received a physical exam by a pediatric neuromuscular physician or physician's assistant as well as complete blood count, urinalysis, complete metabolic panel, INR, PT and PTT. Additionally, there were periodic standardized assessments by a trained research physical therapist as required based upon the age of the patient, insurance payor needs for coverage of the drug, as well as patient availability. The use

of CSF samples and iPSCs was approved by the Medical College of Wisconsin Institutional Review Board (PRO00030075; PRO00025822), the Institutional Biosafety Committee (IBC20120742) and the Human Stem Cell Research Oversight Committee.

RNA extraction and spike-in control assessment from patient CSF samples

CSF samples were immediately frozen after collection and stored at -80°C. CSF samples visibly contaminated with blood were not used in this study. On day of processing, CSF were thawed on ice, centrifuged for 5 minutes at 700 x g to remove any contaminating debris, and aliquoted into fresh tubes. 1x 625ul aliquot of each CSF sample was processed immediately for RNA extraction using the mirVana™ PARIS™ RNA and Native Protein Purification Kit (Ambion), following the liquid sample preparation according to manufacturer's instructions. Before the addition of the denaturing solution, 1ug of MS2 RNA carrier (Sigma) was added to each sample to facilitate RNA recovery. Prior to acid-phenol:chloroform addition, 3.5ul of miRNeasy Serum/Plasma Spike-In Control (miR-39, 1.6×10^8 copies; Qiagen) was added to each CSF sample. qPCR to detect this miR-39 spike-in control was performed post extraction to estimate RNA recovery. cDNA was generated from CSF isolated RNA and a control RNA sample spiked with miR-39 (1×10^8 copies/ul) using the miScript HiSpec kit (Qiagen); dilutions were created from the control cDNA sample spiked with miR-39 (1×10^6 - 1×10^3 copies) to generate a standard curve. The miR-39 spike-in control copies in CSF samples ranged from 40,257-986,469 copies; these data were used to normalize RNA input across CSF samples for RT-qPCR experiments.

RT-qPCR array

RNA samples were DNase treated using the TURBO DNA free kit (Ambion) prior to cDNA synthesis. The RT² PreAMP cDNA synthesis kit (Qiagen) was used with the Human Aging RT² PreAMP Pathway Primer Mix. Samples were applied to the Human Aging RT² Profiler PCR arrays (Qiagen) and run on Bio-Rad CFX384 real time thermocycler. Samples passed quality controls built into the array plates and target gene Cq values on qPCR array were normalized to the HPRT1 house keeping gene values. Ct values observed in the latest post-treatment CSF samples collected at the time of this study for each patient were normalized to pre-treatment (CSF1) samples to calculate the relative fold change (ddCT) in gene expression.

microRNA qPCRs

cDNA for microRNA qPCR experiments was generated from CSF RNA samples using the miScript II RT kit. Preamplification on cDNA was performed using the miScript PreAMP kit using the following primer sets (Qiagen): Hs miR146a_1 (M00003535), Hs miR23a_2 (M00031633), Hs_mir-218_1 (MS00006769), Hs_mir-9_1 (MS00010752), Hs_mir-132_1 (MS00003458) and Hs_mir-431_1 (MS00004200). Hs miR103a_1 (M00031241) was included to be used as a housekeeping microRNA for qPCRs. PreAMP primer sets for miR-16 (determining dilution factor) and miR-16 (estimated efficiency of preamplification reactions) were also included in the amplification reactions; CSF samples did not require further dilution and all samples passed the preamplification quality control. qPCRs for each target microRNA was performed using miScript SYBR Green PCR kit (Qiagen) using a Bio-Rad CFX384 real time thermocycler. In this analysis, we used CSF1 (pre-treatment), CSF4 (4th nusinersen dose) and the latest post-treatment CSF samples collected at the time of this study for each patient. All samples were normalized to pre-treatment samples (CSF1) for each patient to calculate the relative fold change in expression.

Stem cell culture, motor neuron differentiation and mir146a mimic treatment

Previously characterized induced pluripotent stem cell lines (iPSCs) from 2x SMA Type 1 patients (7.12 and 3.6) and 2x healthy individuals (21.8, 4.2; 4.2 is the parent of 3.6) were used in this study (19, 20). iPSCs maintenance cultures, motor neuron differentiation and microRNA treatments were performed as previously described (19, 21). Briefly, on Day 28 of motor neuron differentiation, cells were treated for 48 hours with 40nM miR-146a-5p mimic (Ambion) or mirVana miRNA mimic negative control 1 (Ambion).

EndoPorter (Gene Tools, LLC) was used as the transfection reagent. Cells were collected for RNA sequencing or analyzed in multi-electrode array (MEA) experiments.

RNA sequencing of motor neuron differentiations

Cell pellets were processed using the RNeasy kit (Qiagen) according to manufacturer's guidelines; on-column DNaseI treatment (Qiagen) was also performed on all samples. RNA concentrations and RIN values were obtained using the RNA ScreenTape kit and the TapeStation system (Agilent); all samples had a RIN score >9 with clear 18S and 28S peaks. ERCC Spike-In Controls (Invitrogen) were added to RNA samples (input RNA was 100ng per sample) prior to processing sample with the NEBNext Poly(A) mRNA Magnetic Isolation Module (NEB #E7490), NEBNext Ultra II RNA Library Prep Kit for Illumina (NEB # E7770) according to manufacturer's protocol. NEBNext Multiple Oligos for Illumina Set 1 (NEB #E7335), 2 (NEB #E7500) and 3 (NEB #E7710) were used to create unique identifiers for each cDNA library sample. Quality of cDNA libraries were assessed using the DNA 100 Chip kit and TapeStation system (Agilent). Single and pooled libraries were assessed using the NEBNext Library Quant kit for Illumina (NEB #E7630), Bio-Rad CFX384 real time thermocycler and calculated using the NEB qPCR webtool (<https://nebiocalculator.neb.com/qPCR>). On the day of sequencing, samples were denatured and diluted following the Illumina NextSeq system Denature and Dilute Libraries Guide using the bead-based normalization method with PhiX library control. Samples were sequenced (20-30 million read depth, 38bp paired end reads) on the Illumina NextSeq system. FASTQ files were processed using Expression count (STAR) pipeline in Basepair before performing principal component analysis and DeSeq2 RNA seq analysis. Gene Ontology analysis was performed using the gprofiler web server (22).

Multi-electrode array

On day 14 of motor neuron differentiation, neurospheres were dissociated in TrypLE (Life Technologies) and plated on to 0.1% PEI coated CytoView MEA 48 well plates (Axion Biosystems) at 50,000 cells per well in a 10ul droplet over the electrodes. 20µg/ml laminin was supplemented into the motor neuron maturation medium (composition described in (19, 21)) to aid cell attachment. After 1-hour incubation, wells were flooded with 300ul motor neuron maturation medium; medium was replaced every 3 days. Spontaneous activity recordings were performed using the Axion Biosystems Maestro System on a stage maintained at 37°C. 1-minute recordings were taken before (Day 28) and after (Day 30) treatment. Weighted mean firing rate (WMFR; number of spikes (i.e. action potentials) from active electrodes (>5 spikes) over the duration of analysis) measured in Hz was used to assess motor neuron activity in this study. Recordings, data collection and waveform analyses were completed using Axis (Axion Biosystems). WMFR treatment data was normalized to UTX control for each line.

Statistics, rigor and reproducibility

For the qPCR array, 6x Type 1, 6x Type 2 and 2x Type 3 SMA patient samples were analyzed; for the microRNA qPCRs, 11x Type 1, 15x Type 2, 9x Type 3 SMA patient samples were analyzed. Samples were run in technical duplicates and Ct values were averaged for downstream analysis. For the RNA seq experiments, motor neurons were generated from 2x SMA Type 1 patients and 2x healthy individuals; 2-3 individual differentiation samples were included in the analysis. -log10 adjusted p-values (<0.05) and log2 fold change (<-1 or >1) thresholds were considered statistically significant for the DeSeq2 analysis. The same 4 cell lines were run in technical triplicates on the MEA plates; data are from 2x plates.

Results

Surplus CSF was used in this study collected from SMA patients receiving intrathecal nusinersen injections during the course of standard clinical care. Table 1 details the patients' gender, age, CSF samples analyzed in this study and motor functioning test scores. Clinically, all patients in this study receiving treatment did well without decline in feeding, respiratory support requirements or motor activities of daily living. One patient, SMA006, did transfer care to another center resulting in a lack of further assessments, while patient SMA001 died suddenly in her sleep without an overt decline or infection noted

prior; no adverse effects from the medication were noted. Regarding the standardized assessments, while they did not correlate directly to the therapeutic infusions temporally, they did demonstrate an overall improvement in patient motor functioning. Patient SMA003 was an exception; the patient's strength was improving but overall, there was a decline in the Hammersmith score secondary to the patient developing contractures from a lack of reliable stretching.

We used a quantitative RT-PCR (qRT-PCR) array approach to begin assessing novel extracellular mRNA biomarkers associated with inflammatory and stressor responses in SMA patient CSF samples. Across SMA Type 1 (Fig. 1Ai), Type 2 (Fig. 1Bi) and Type 3 (Table 2) patient samples, we identified a total of 48 upregulated genes, involved in immune responses (FCER1G, CD14), inflammatory signaling (C3AR1, TOLLIP, S100A8, S100A9), cell cycle regulation (CDKN1C, RAP1A), genomic stability (SIRT6) and apoptosis (CASP1, CLU, PDCD6). Furthermore, genes encoding fibril-forming collagen proteins (COL1A1 and COL3A1) were also found to be upregulated in Type 1 and 2 patients, while the TGF- β signal transducer, SMAD2, was found to be upregulated in both Type 2 and 3 patients. 46 downregulated genes were identified across all SMA disease types in samples post-nusinersen treatment (Fig 1A-Bii; Table 2); intriguingly, ANGEL2, a 2',3'-cyclic phosphatase involved in RNA processing and unfolded protein response (UPR) transcription factor, XBP1, mRNA splicing (23), was the only gene to show consistent downregulation across all SMA disease types. ELAVL1, a known binding partner of SMN, also showed a downregulated expression trend, but only in SMA Type 1 patient samples. We did note some overlapping genes between the upregulated and downregulated datasets, dependent upon the SMA disease type. Gene Ontology (GO) analysis revealed an overall enrichment of proteolysis and metabolic processes terms within the upregulated genes (Fig. 1C), whereas astrocyte and glial cell development GO terms were particularly enriched within the downregulated genes (Fig. 1D).

We next assessed microRNAs as potential biomarkers in the SMA pre- and post-nusinersen treated CSF samples, focusing on those that have been previously been implicated in SMA disease pathology (Fig. 2). We observed an overall upregulated trend in expression across all microRNAs in patient samples, with CSF1 represents the baseline microRNA expression prior to treatment (dotted lines in each graph). In some patients there was an earlier increase in microRNA expression (detected in CSF4/5 samples), including miR-132 (Fig. 2A), miR-218 (Fig. 2B) and miR-9 (Fig. 2C), whereas other microRNAs showed a more gradual change in expression across the nusinersen treated samples (Fig. 2D-F). This trend was mainly observed in Type 1 and 2 patient samples, who clinically responded well to treatment (Table 1). This is an encouraging trend for microRNAs that are typically downregulated in SMA, including miR-132, miR-218, miR-9 and miR-23a (Fig. 2A-D). miR-431 expression is increased in SMA pathology, but it appears to remain relatively unchanged post-nusinersen treatment due to the low fold change levels in expression observed (Fig. 2E). Similarly, increased miR-146a expression is associated with SMA pathology; however, post-nusinersen treated CSF samples in SMA patients continued to show increased expression of this microRNA (Fig. 2F).

We have previously found that astrocyte-produced miR146a induces a reduction in choline acetyltransferase (ChAT) expression and neurite outgrowth in iPSC-derived motor neuron cultures (19). Due to the detection of inflammatory and astrocyte and glial development GO terms and the increased expression of astrocyte-associated miR-146a in post-nusinersen treated CSF samples, we used mRNA sequencing to further dissect molecular mechanisms that may be contributing to motor neuron malfunction and loss in SMA. Principal component analysis of all motor neuron samples demonstrates clustering by differentiation culture replicates (Fig. 3A). Importantly, miR146a treated samples in all clusters closely align with untreated (UTX) or negative mimic treated samples, which was also reflected in the DESeq2 comparative analysis where no statistically significant differentially expressed genes were determined ($-\log_{10}$ adjusted p value < 0.05). Previous reports have suggested that microRNAs are responsible for fine-tuning gene expression and thus microRNA expression modification may have more subtle effects (24). We therefore analyzed genes without the p value correction (p value < 0.05), but with robust fold change in expression ($\log_2FC < -1$ or > 1) to identify 163 and 121 differentially expressed genes comparing healthy UTX vs miR-146a treated samples and SMA UTX vs SMA miR146a treated

samples, respectively (Table 3). In both datasets, a larger number of downregulated genes were observed (149 genes healthy UTX vs healthy miR-146a treated; 115 genes SMA UTX vs SMA mir146a treated). GO analyses on these downregulated genes showed enrichment of terms related to extracellular matrix (ECM), metalloproteinase activity, collagen-containing ECM, catabolic processes and plasma membrane components (Fig. 2B and C), with heatmaps highlighting downregulated genes found in the GO terms (Fig. 2D). Of particular interest was the identification of genes encoding matrix metalloproteinases (MMP17, 10, 1), a disintegrin and metalloproteinase (ADAM29) with thrombospondin repeats (ADAMTS2, 9, 3 14, ADAMTS2L2), and other ECM-related genes (e.g. TNC, THBS2, HAPLN1, NEDD9, ITGA4) because of their known role at the perineuronal net and interactions at the synapse. This led us to look further for synaptic related genes within the downregulated datasets, to which we identified genes associated with dendritic spine formation and stability (SYT6, GPX3), axonal guidance and outgrowth (PLXNB3, NGEF, SPON2), glutamate transporters and receptor subunits (SLC17A8, GRID2, GRM8, GRIN3A) and potassium voltage gated ion channels (KCNE4, KCNQ3, KCNQ5). We also found a downregulation of genes needed to maintain neuronal health against oxidative damage (GPX3, ENC1) and through neurotrophic factor signaling (NTRK1, GFRA2). Intriguingly, synapse was an enriched GO term when analyzing known miR-146a gene targets (Fig. 2F); among these established miR-146a targets, we identified the vesicular glutamate transporter, SLC17A8, within our downregulated gene sets and identified genes with similar functions to known miR-146a targets (e.g. MMP and ADAMTS proteases, and SYT6).

To assess if the downregulation of synaptic genes due miR-146a exposure could impact motor neuron function, we used a multi-electrode array (MEA) approach to assess spontaneous action potentials in UTX, negative mimic and miR146a mimic treated iPSC-derived motor neurons (Fig. 4A). Motor neuron action potentials were detected beginning at 8 days after plating (Fig. 4B). Prior to treatment, there was no significant difference observed in the weighed mean firing rate (WMFR) between healthy and SMA motor neurons, although we did observe a slight increase in the SMA motor neuron activity (Fig. 4C). After 48 hours of miR-146a treatment, WMFR decreased in the healthy motor neurons whereas SMA motor neurons showed increased activity (Fig. 4D). Although not statistically significant, these data still represent an interesting observation regarding intrinsic synaptic differences between healthy and SMA motor neurons. We returned to the transcriptome data to compare healthy vs SMA motor neuron samples to look for difference in synaptic gene expression (Fig 4E; Table 3). Similar to the miR-146a treated samples, we saw a downregulation in ECM-related genes and those found in the perineuronal nets of the synaptic cleft (TNC, THBS2) in SMA patient-derived motor neurons. We also observe an increase in several neurotransmitter receptors (SYNDIG1, GRM2, GRIK1), neurotransmission release and synaptic vesicle trafficking (RPH3A) that could be linked to SMA motor neuron hyperexcitability.

Discussion

Despite the significant progress made in SMA therapy development, there remains a lack of reliably detectable biomarkers in patient biospecimens that can be used to track physiological change post-treatment over time. CSF is in direct contact with the primary diseased cells in SMA, and therefore represents a promising biospecimen to be used in biomarker discovery. Due to the intrathecal delivery of nusinersen, routine detection and analysis of biomarker trends in surplus CSF would be a feasible approach to perform in the clinic. For this study we focused on characterizing neurodegenerative biomarkers to provide a more disease-specific measurement to monitor CNS cellular health in SMA.

Clinically, all patients in this study receiving treatment did well, which is consistent to what has been seen in other patients treated with nusinersen and is contrary to the natural history of the disease (25, 26). Correlating these clinical observations to our biomarker screening, which overall showed continued upregulation of cellular stress genes but improvements in motor neuron-associated microRNA expression, further highlights the importance of understanding mechanisms driving cell recovery and survival and when improvements at the molecular level can be observed after nusinersen treatment. Our data also suggest that glial health is an important aspect to monitor in SMA patients in disease state and

post-treatment, as demonstrated by the downregulated genes in the array and the continued elevated levels of astrocyte-secreted miR-146a in post nusinersen treated CSF samples. Post-mortem studies reveal that nusinersen is detectable glial cells throughout the CNS and spinal cord (27), but downstream molecular events after SMN targeting in human CNS cells have yet to be established. Our data suggest that longitudinal assessment of cellular function after prolonged nusinersen treatment (possibly greater than 13 doses; latest sample of this study) are needed beyond the motor function scores to fully elucidate changes in disease pathology.

While we found overlapping gene expression trends in the qRT-PCR array data for patients with the same disease severity, a number of genes were uniquely upregulated or downregulated in individual patient samples, and most of the genes analyzed did not show consistent expression trends across all patient samples (e.g. the same gene was upregulated in some samples, but downregulated in others). A similar observation was made in a proteomics study assessing neurodegenerative biomarkers in SMA CSF samples; no consistently differentially expressed proteins were found in response to nusinersen treatment across their dataset (15). The only consistent observation across all SMA patient samples post nusinersen treatment within our array data was the downregulation of ANGEL2, a recently identified CCR4 deadenylase with 2',3'-cyclic phosphatase activity involved in RNA processing (23). ANGEL2 is thought to antagonize the mRNA splicing of XBP1, a transcription factor that regulates UPR during ER stress (28). Previous transcriptome data revealed SMA patient iPSC-derived motor neurons show upregulated expression of UPR genes, including spliced XBP1, compared to control iPSC-derived motor neurons (29). Downregulation of ANGEL2 within our dataset suggests cellular stress may still be apparent in patients even after nusinersen treatment. Future studies are needed to explore the potential mechanism involving ANGEL2 in SMA and its use as a biomarker in patient CSF samples.

Seems microRNAs are important RNA processing regulators, potentially linked to SMN function (30), can act as disease modifiers (31) and are relatively stable in biofluids, they represent good biomarker candidates. SMA patient serum has mainly been used to investigate microRNA levels at baseline (32) and after nusinersen treatment (33); seems microRNA specificity may differ depending on the tissue type (e.g. muscle vs CNS) and the type of biospecimen (e.g. serum vs CSF) analyzed, we focused on detecting microRNAs relevant to CNS cellular health in CSF samples. In most of the post-treated samples, we observed an overall increased expression trend of miR-9 and miR132, previously shown to be downregulated in SMA spinal cord tissue (32) and associated with neurite outgrowth delays (34-36). The same increased expression was also observed for miR-218 and miR23a normally downregulated in neuromuscular disorders, correlating with motor neuron synaptic defects and hyperexcitability (37), and motor neuron survival and neuroprotection (38). Our data are concordant with a previous study showing the improved increased expression of microRNAs (e.g. miR-132) in the spinal cords of mild and severe SMA mice after receiving PMO25 antisense oligonucleotide treatment (32). Together, this supports the notion that microRNA detection in CSF could serve as a useful way of monitoring physiological changes in response to treatment.

We have previously shown that SMA iPSC-derived astrocytes show abnormally elevated expression and secretion of miR-146a, which is sufficient to induce a decrease in the percent of ChAT+ motor neurons (19). The continued upregulation of miR-146a in CSF samples post nusinersen treatment prompted further investigation into mechanistic mediators via RNA seq, which could be involved in miR-146a induced motor neuron damage. Interestingly, the DeSeq2 analyses revealed a downregulation of genes related to extracellular matrix proteins, which complements findings from other human transcriptomic data comparing healthy and SMA iPSC-derived motor neurons (29). Many of the extracellular matrix associated genes within our dataset have been previously implicated at the synaptic perineuronal net, including HAPLN1 that was previously reported to be downregulated in SMA Type 1 and 3 patients (39), and those with altered expression in other neurodegenerative diseases, such as matrix metalloproteinases and NEDD9 (40, 41). Encouragingly, a number of these genes are validated miR-146a targets or have similar functional roles to known miR-146a targets, which implicates miR-146a-mediated regulation in synaptic function (42, 43). We also found a number of genes related to astrocyte

mediated synaptic regulation, such as tenascin C and thrombospondin 2, which both play important roles at the perineuronal nets to support synaptic form and function (44). Additionally, evidence suggests that glial microRNAs can regulate ECM molecules, such as brevican (45), a major component of perineuronal nets. Therefore, we propose that miR-146a may be causing downregulation of synaptic related ECM genes and ultimately affecting perineuronal net regulation at the SMA motor neuron synapses.

Using a MEA approach, we also investigated the functional impact of miR-146a on synaptic activity of iPSC-derived motor neurons. Although we did observe a level of variability within the experiments, overall miR-146a treatment decreased firing rate of healthy motor neurons, whereas it increased activity in the SMA motor neurons. This was an intriguing finding in relation to the hyperexcitability phenotype previously identified in SMA motor neurons; evidence suggests this hyperexcitability phenotype could be a SMN-dependent motor neuron cell-autonomous (46) or non-cell autonomous phenotype (47). Our transcriptomic (healthy vs SMA samples; Fig. 4E) and MEA data suggest there may be a motor neuron intrinsic mechanism, seems we detect upregulated neurotransmitter receptor genes and increased baseline spontaneous action potential activity in SMA samples, in addition to observing opposite trends in miR-146a treated healthy and SMA-derived motor neuron WMFRs. However, together with the abnormally elevated miR-146a secretion by SMA astrocytes (19), the miR-146a transcriptome data also suggest a role of astrocyte-secreted factors causing dysfunction at motor neuron synapses in SMA. The exact pathways and downstream events that involve miR-146a and downregulated expression of these genes in SMA remains to be fully established, but our data begin to identify possibilities. For example, direct targets of miR-146a regulation, as previously demonstrated for a number of pre- and post-synaptic terminal genes (SYT1, NLG1) and those involved in synaptic plasticity (MAP1B) and glutamatergic neurotransmission (GRIA3, AMPARs, SLC17A8) may all contribute to motor neuron malfunction (42, 43, 48). The downregulation of neurotrophic factors (NTRK1, GFRA2) by miR-146a, could in turn affect the expression of motor neuron voltage-gated ion channels (49). A number of perineuronal net ECM associated genes downregulated in the miR146a treated motor neuron transcriptomes are known to play an active role in pre- and post-synaptic scaffolding (proteoglycans), synaptic stability and organization (cadherins, integrins), plasticity (tenascins), and synaptic remodeling (matrix metalloproteinases) to influence neurotransmitter receptor and ion channel activity (50). Therefore, there could be mechanistic links that involve ECM composition at perineuronal nets and regulation of their genes by astrocyte secreted miR-146a, ultimately impacting motor neuron expression of neurotransmitter and ion channel genes and leading to diminished functioning in SMA (Fig. 4F).

Together, our data demonstrate that SMA patient CSF exhibits altered transcriptional and glia-associated microRNA profiles indicative of sustained motor neuron stress and synaptic malfunction even with nusinersen treatment. Considering that treated SMA patients are now living long past the natural history of this disease, additional screening and profiling should be pursued to elucidate robust measures of therapeutic efficacy.

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Author Contributions

Author contributions: E.W.: Acquisition and analysis of data, manuscript writing and editing. R.J.R.: Data acquisition. M.M.H.: Data acquisition and analysis. A.D.E.: Conception and design study, data analysis, manuscript writing and editing.

Conflicts of interest statement:

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Figure legends

Table 1. List of patient samples used in this study and motor function scores. CHOP-I-SCORE: The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE: Hammersmith Infant Neurological Examination; HFMSE: Hammersmith Functional Motor Scale Expanded; RULM: Revised Upper Limb Module.

Figure 1. Screening for mRNA biomarkers in SMA patient CSF samples using a RT-qPCR array. Pre-amplified cDNA samples from SMA Type 1 (A) and Type 2 (B) patient CSF samples were run on RT² Profiler PCR array (SMA Type 3 patient data included in Table 2). Upregulated (i) and downregulated (ii) genes were detected; gene expression of latest post-nusinersen treated CSF samples (e.g. CSF 11) was normalized to pre-treatment gene expression (i.e. CSF1) for each patient. The Venn diagrams show the number of overlapping genes and genes that are specific to each patient, and the tables detail the overlapping genes and their relative fold changes $\pm$ standard deviation (SD) compared to CSF1 (A-B). Gene ontology analyses were performed on upregulated genes (C) and downregulated genes (D) across all SMA patient samples.

Table 2. Gene lists of upregulated and downregulated genes from RT-qPCR array

Figure 2. Screening for microRNA biomarkers in SMA patient CSF samples via RT-qPCR. Pre-amplified cDNA samples from SMA Type 1 (blue data points), Type 2 (pink data points) and Type 3 (black data points) patient CSF samples were screened for previous microRNAs implicated in SMA disease pathology. miR-132 (A), miR-218 (B), miR-9 (C), miR-23a (D), miR-431 (E) and miR-146a (F) expression is represented in the graphs as relative fold change; CSF4 and latest post-nusinersen treated CSF samples were normalized to pre-treatment samples (CSF1).

Figure 3. RNA seq analysis of iPSC-derived motor neurons with mir146a treatment. DeSeq2 analysis was performed on all motor neuron samples including untreated (UTX), negative miR mimic (neg miR) and miR-146a treated from both control and SMA iPSC lines. This incorporates a Principal Component Analysis (A) to assess the variance between samples based on gene expression. Gene ontology (GO) analysis was performed on those differentially expressed genes (p value<0.05) that were downregulated (log2 fold change) in control UTX vs miR-146a treated samples (B) and SMA UTX vs SMA miR-146a treated samples (C). The heatmaps highlight those genes encoding extracellular matrix proteins (some related to the synapse) (D) and genes encoding neuronal health/synapse related proteins (E) that are downregulated in control and SMA miR-146a treated samples, respectively. GO analysis was additionally performed on a gene list of known miR-146a targets (F) which also showed an enrichment of GO terms associated with synapse and neuron projection morphogenesis.

Table 3. RNA seq differentially expressed genes (healthy UTX vs healthy miR-146a, SMA UTX vs SMA miR-146a, healthy UTX vs SMA UTX). padj; adjusted p-value.

Figure 4. Multi-electrode array (MEA) analysis on miR-146a treated iPSC-derived motor neurons. To test the functional effects of miR-146a at the synapse, iPSC-derived motor neurons were plated on to the electrodes of MEA plates (A). Action potentials could be detected in both healthy and patient cells (B). Weighed mean firing rate (WMFR) was measure before (C) and after (D) 48-hour treatment of either normal medium (UTX), 40nM miR-146a mimic or 40nM of neg miR mimic (neg mimic). Data for each line are normalized to WMFR for UTX sample. (E) DeSeq2 analysis reveals several ECM/ECM-synapse related genes that are downregulated in SMA motor neurons (green datapoints), whereas genes encoding synaptic-related genes are upregulated in SMA motor neuron (red datapoints). (F) Schematic of potential disease mechanism involving astrocyte secreted miR-146a at the perineuronal net of motor neuron synapses.

A SMA Type 1 patients

(i) Upregulated genes

Patient 1 (F, 9 months)
CSF1 vs CSF8

Patient 6 (F, 7 months)
CSF1 vs CSF4

Overlapping genes	Patient 1	Patient 6	Patient 17
FCER1G	89.4 ± 0.01	106.5 ± 0.1	
C3AR1	18.8 ± 0.3	14.9 ± 0.6	
COL1A1		2.8 ± 0.1	2.3 ± 0.2
CDKN1C		624.6 ± 0.1	82.0 ± 0.6
CD14		64.0 ± 0.6	179.8 ± 0.3
COL3A1	5.0 ± 0.6		2.9 ± 0.3
CASP1	137.7 ± 0.1		66.3 ± 0.6
CLU	51.1 ± 0.2		37 ± 0.02
S100A8	61.9 ± 0.3		2 ± 0.1
RAP1A	105.0 ± 0.4		7.1 ± 0.3

(ii) Downregulated genes

Patient 1 (F, 9 months)
CSF1 vs CSF8

Patient 6 (F, 7 months)
CSF1 vs CSF4

Overlapping genes	Patient 1	Patient 6	Patient 17
C1QB	0.2 ± 2.1	0.6 ± 0.5	0.4 ± 1.8
ANGEL2	0.5 ± 0.3	0.3 ± 0.7	0.3 ± 0.04
MBP	0.005 ± 0.1	0.3 ± 0.1	
ELAVL1	0.02 ± 1.5	0.01 ± 0.2	
ZBTB10	0.01 ± 0.1	0.02 ± 0.4	
SIRT3	0.008 ± 0.1	0.01 ± 0.2	
JAKMIP3		0.2 ± 0.4	0.02 ± 2.0
WRN	0.008 ± 0.1		0.007 ± 0.1

B SMA Type 2 patients

(i) Upregulated genes

Patient 18 (F, 3yrs)
CSF1 vs CSF10

Patient 2 (F, 3yrs)
CSF1 vs CSF13

Overlapping genes	Patient 2	Patient 18	Patient 10
SMAD2	118.5 ± 0.8	79.9 ± 0.1	47.8 ± 0.5
PDCD6	45.8 ± 0.9	173.5 ± 0.06	
COL1A1	101 ± 0.02	3.2 ± 0.2	
S100A9	135 ± 0.006	41.8 ± 0.1	
TOLLIP	102.8 ± 0.5	156.1 ± 0.4	
ZBTB10	21.1 ± 0.4	12.2 ± 0.8	
NDUFB11	92.7 ± 0.9	3.3 ± 0.02	
PHF3	221.1 ± 0.15		233.3 ± 0.6
MBP	46.4 ± 0.04		22.5 ± 0.02
CDKN1C	189 ± 0.3		204.8 ± 0.2

(ii) Downregulated genes

Patient 18 (F, 3yrs)
CSF1 vs CSF10

Patient 2 (F, 3yrs)
CSF1 vs CSF13

Overlapping genes	Patient 2	Patient 18	Patient 10
ANGEL2	0.57 ± 0.15	0.27 ± 0.1	0.5 ± 0.04
CD163	0.01 ± 0.01	0.04 ± 0.04	
WRN		0.06 ± 0.04	0.01 ± 0.1
RAP1A		0.01 ± 0.04	0.02 ± 0.1
FCGR1A		0.02 ± 0.04	0.06 ± 0.1
VWA5A	0.01 ± 0.01		0.01 ± 0.1

C Enriched GO terms (upregulated genes)

D Enriched GO terms (downregulated genes)

A**miR-132** **B****miR-218** **C****miR-9** **D****miR-23a** **E****miR-431** **F****miR-146a**

C Before treatment (Day 28)

D After treatment (Day 30)

E DE genes (control vs SMA motor neurons)

F

Patient	SMA Type	Gender	Age	Samples	Motor function scores									
					Scores nearest CSF1	Scores nearest CSF4	Scores nearest CSF5	Scores nearest CSF6	Scores nearest CSF8	Scores nearest CSF9	Scores nearest CSF10	Scores nearest CSF11	Scores nearest CSF12	Scores nearest CSF13
SMA006	1	Female	7 months	CSF 1, 4	CHOP-I-SCORE: 22/64 HINE SCORE: 27/78									
SMA017	1	Female	2 months	CSF 1, 4, 5	CHOP-I-SCORE: 10/64 HINE SCORE: 28/78		CHOP-I-SCORE: 26/64 HINE SCORE: 35/78							
SMA001	1	Female	9 months	CSF 1, 4, 8	CHOP-I-SCORE: 22/64 HINE SCORE: 29/78				CHOP-I-SCORE: 37/64 HINE SCORE: 29/78					
SMA021	1	Female	20yrs	CSF 1, 4, 5	Physical therapy tests not obtained									
SMA002	2	Female	3yrs	CSF 1, 4, 13	HFMSE SCORE: 3/66 RULM SCORE: 10	HFMSE SCORE: 4/66 RULM SCORE: 12								HFMSE SCORE: 10/66 RULM SCORE: 14
SMA003	2	Female	11yr	CSF 1, 4, 13	HFMSE SCORE: 10/66 RULM SCORE: 19/38	HFMSE SCORE: 10/66 RULM SCORE: 21								HFMSE SCORE: 6/66 RULM SCORE: 14
SMA022	2	Male	11yrs	CSF 1, 4, 6	HFMSE SCORE: 6/66 RULM SCORE: 20									
SMA018	2	Female	3yrs	CSF 1, 4, 10	CHOP-I-SCORE: 38/64 HINE SCORE: 38/78 HFMSE SCORE: 11/66	CHOP-I-SCORE: 43/64 HFMSE SCORE: 14/66 RULM SCORE: 14					HFMSE SCORE: 15/66 RULM SCORE: 15			
SMA010	2	Male	13yrs	CSF 1, 4, 11	HFMSE SCORE: 2/66 RULM SCORE: 6	HFMSE SCORE: 2/66 RULM SCORE: 8						HFMSE SCORE: 2/66 RULM SCORE: 7		
SMA007	3	Male	14yrs	CSF 1, 4, 9	HFMSE SCORE: 51/66 RULM SCORE: 22	HFMSE SCORE: 46/66 RULM SCORE: 23				HFMSE SCORE: 52/66 RULM SCORE: 27				
SMA023	3	Male	4yrs	CSF 1, 4, 6	HFMSE SCORE: 49/66 RULM SCORE: 28/37	HFMSE SCORE: 52/66 RULM SCORE: 32								
SMA004	3	Male	9yrs	CSF 1, 4, 12	HFMSE SCORE: 39/66 RULM SCORE: 27	HFMSE SCORE: 40/66 RULM SCORE: 27							HFMSE SCORE: 39/66 RULM SCORE: 32	

Table 1. List of patient samples used in this study and motor function scores.

Upregulated genes from qPCR array			
Patient	Gene	CSF samples	
		Fold change (CSF1 vs CSF8)	Standard deviation
SMA Type 1 Patient 1	CASP1	137.6780611	0.077066231
	RAP1A	105.0277355	0.396821273
	FCER1G	89.4378156	0.01024327
	SMAD2	75.600257	1.072265243
	S100A8	61.92780669	0.345332247
	CLU	51.10488666	0.242735864
	TINF2	31.1294647	0.385072282
	COL3A1	4.993260377	0.567399927
		Fold change (CSF1 vs CSF4)	Standard deviation
SMA Type 1 Patient 6	CDKN1C	624.5714924	0.113307
	FCGR1A	114.1071797	0.353113154
	LYZ	109.0805366	0.17213043
	FCER1G	106.5105179	0.078189651
	CD14	63.99338544	0.626886034
	TMEM135	54.11798305	1.054954958
	ELP3	46.86267237	1.866680798
	C3AR1	18.75636511	0.27921538
	PDCD6	3.179984491	0.273234679
	COL1A1	2.791978761	0.141905159
	ANXA5	1.80016017	0.178070963
		Fold change (CSF1 vs CSF5)	Standard deviation
SMA Type 1 Patient 17	CD14	179.8169828	0.329436003
	TOLLIP	92.04404226	0.720422074
	MBP	89.23893429	0.155628565
	TPP1	86.18803061	0.116520265
	CDKN1C	82.01489092	0.562600756
	EML1	81.69333115	0.271808028
	VPS13C	68.11989442	0.352171864
	CASP1	66.34249587	0.578650204
	HSF1	52.15679859	0.044524139
	CLU	37.00182299	0.02191813
	POT1	33.94264604	0.360925318
	PHF3	32.10791118	1.07868608
	MRPL43	21.92243282	0.29517183
	GSTA1	20.36415497	0.278336583
	LMNA	15.40901632	1.248743278
	C3AR1	14.92290717	0.551025991
	TLR2	9.4232939	0.767708349
	RAP1A	7.106411083	0.294887763
	ZFR	3.105381571	0.310935775
	COL3A1	2.857957726	0.298002514
	COL1A1	2.333934487	0.1792467
	S100A8	2.04577801	0.113949073

	LSM5	1.63997989	0.225427155
	CFH	1.583413177	0.195423902
	S100A9	1.354421064	0.392080053
	TLR4	1.335493175	0.366182584
	Fold change (CSF1 vs CSF10)		Standard deviation
SMA Type 2 Patient 18	PDCD6	173.5143332	0.057659607
	TOLLIP	156.1380931	0.431907451
	SMAD2	79.91170427	0.096224827
	ELP3	45.722541	0.381249406
	S100A9	41.78844081	0.095031657
	LMNB2	21.6469886	0.346593572
	GSTA1	18.78526285	0.595614823
	ZBTB10	12.21862039	0.762737035
	NDUFB11	3.298037236	0.021180594
	COL1A1	3.184279403	0.23708451
		Fold change (CSF 1 vs CSF13)	Standard deviation
SMA Type 2 Patient 2	FCGR1A	584.1383638	0.355577169
	ANXA5	531.8858819	0.147952986
	TFB1M	258.0360206	0.095628785
	CLU	225.2235497	0.551154577
	PHF3	221.150279	0.155725009
	SIRT1	190.8595581	0.200595582
	TMEM135	190.4471571	0.158214718
	CDKN1C	189.0623708	0.250601367
	S100A9	135.0406671	0.006485973
	EP300	130.1434965	0.442934195
	SMAD2	118.502489	0.793600312
	ELAVL1	103.0557968	0.307191066
	TOLLIP	102.7914085	0.549177745
	COL1A1	100.9872348	0.018083017
	ZNF25	96.99897278	0.242291511
	NDUFB11	92.66278432	0.856761758
	MRPL43	88.59719613	0.947594479
	LSM5	69.95014131	0.114391758
	LMNA	53.77257768	0.108234293
	MBP	46.42815795	0.040258552
	PDCD6	45.76825825	0.886061029
	ZBTB10	21.14065574	0.413692515
		Fold change (CSF1 vs CSF11)	Standard deviation
SMA Type 2 Patient 10	FCGBP	417.6680263	0.010656394
	PHF3	233.3443559	0.579730693
	CDKN1C	204.7861992	0.244733551
	SIRT3	58.93410061	0.333015907
	SMAD2	47.80902195	0.486909747
	MBP	22.49584673	0.019454875
	TERF2	11.02807011	0.094799276

	SIRT6	4.794880595	0.191212338
	Fold change (CSF1 vs CSF9)		Standard deviation
SMA Type 3 Patient 7	S100A8	98.42173392	0.043989086
	POLRMT	80.29445387	0.475298452
	SIRT1	77.8899168	0.146657723
	TINF2	70.94753706	0.015234193
	SIRT6	46.80597869	0.670577912
	FCER1G	40.38169017	0.416247735
	LMNB2	37.95351574	0.333048049
	SMAD2	34.6404783	0.693343932
	RAP1A	31.79333196	0.962911765
	CDKN1C	7.696561994	0.210202678
	COL3A1	1.970087049	0.034445243
Downregulated genes from qPCR array			
Patient	Gene	CSF samples	
		Fold change (CSF1 vs CSF8)	Standard deviation
SMA Type 1 Patient 1	ANGEL2	0.47560534	0.324373876
	C1QB	0.217218762	2.147239377
	ELAVL1	0.016014869	1.494078081
	SIRT1	0.010019592	0.149775637
	ZBTB10	0.009851439	0.149775637
	WRN	0.007996542	0.149775637
	SIRT3	0.007923551	0.149775637
	MBP	0.005150489	0.06821062
	Fold change (CSF1 vs CSF4)		Standard deviation
SMA Type 1 Patient 6	COL3A1	0.644604761	0.240358893
	C1QB	0.582525045	0.452585549
	SNAP23	0.378493734	0.309616138
	MBP	0.3273256	0.097744264
	ANGEL2	0.306683707	0.698132674
	LMNA	0.205893418	0.249621848
	JAKMIP3	0.156796644	0.365855905
	TXNIP	0.063395626	0.15679019
	C5AR1	0.054662431	0.15679019
	BUB1B	0.050576119	0.15679019
	ZBTB10	0.020336097	0.420825512
	EML1	0.019549467	0.15679019
	ZFR	0.01164457	0.15679019
	TINF2	0.009555146	0.15679019
	ELAVL1	0.00902345	0.15679019
	SIRT3	0.006730763	0.15679019
	Fold change (CSF1 vs CSF5)		Standard deviation
SMA Type 1 Patient 17	C1QB	0.421290775	1.849573585
	ANGEL2	0.298832887	0.040388811
	FCGR1A	0.283775686	0.285136655

	FCER1G	0.152380734	0.092837075
	NDUFB11	0.142123082	0.33653961
	JAKMIP3	0.020542569	2.049182279
	LYZ	0.019036281	0.116481975
	PDCD6	0.009608537	0.116481975
	ZNF25	0.008402913	0.116481975
	WRN	0.007055008	0.116481975
	TFB1M	0.005031118	0.116481975
	Fold change (CSF1 vs CSF10)		Standard deviation
SMA Type 2 Patient 18	ANGEL2	0.265039053	0.103281794
	CLU	0.16171658	0.149634744
	WRN	0.061251482	0.038688432
	CD163	0.038358619	0.038688432
	FCGR1A	0.019700529	0.038688432
	MRPL43	0.016099484	1.606029444
	ARL6IP6	0.011497917	0.038688432
	RAP1A	0.009820707	0.038688432
	Fold change (CSF 1 vs CSF13)		Standard deviation
SMA Type 2 Patient 2	ANGEL2	0.574657434	0.150396102
	TINF2	0.218425785	1.196952087
	CD14	0.116463332	1.594650575
	ARID1A	0.014563725	0.012236546
	CD163	0.013182965	0.012236546
	VWA5A	0.006281219	0.012236546
		Fold change (CSF1 vs CSF11)	Standard deviation
SMA Type 2 Patient 10	C1QB	0.915402274	0.114177078
	ANGEL2	0.498470727	0.042179981
	C1QC	0.403954375	1.127620478
	S100A8	0.121075818	0.015522779
	COL3A1	0.077984591	0.345294375
	FCGR1A	0.05878036	0.104202059
	C1QA	0.055116066	0.104202059
	HSF1	0.035261923	0.104202059
	RAP1A	0.02382736	0.104202059
	CASP1	0.022797964	0.104202059
	VWA5A	0.012304053	0.104202059
	WRN	0.011627615	0.104202059
	ANXA5	0.008541818	0.104202059
	TMEM135	0.008306068	0.104202059
	COL1A1	0.006265169	0.256562015
	S100A9	0.002258564	0.104202059
	Fold change (CSF1 vs CSF9)		Standard deviation
SMA Type 3 Patient 7	ANGEL2	0.333549289	0.215145315
	FCGBP	0.216368666	1.906835713
	ZFR	0.106991425	1.087050383
	TERF2	0.09783228	1.128964282

	TLR4	0.059815743	1.582313679
	SIRT3	0.030033526	0.037515975
	COL1A1	0.023115625	1.196391903
	PHF3	0.016128083	0.037515975
	MRPL43	0.014311411	0.037515975
	ZNF25	0.009322887	0.037515975
	FCGR1A	0.00811128	0.037515975
	PDCD6	0.006029665	0.037515975
	ANXA5	0.005820223	0.037515975

Table 2. Gene lists of upregulated and downregulated genes from qPCR array

ontrol UTX vs Control miR-146a (upregulated in control miR-146a)				
Accession number	Genes	log2FoldChange	pvalue	padj
ENSG00000138136.6	LBX1	3.234393449	0.041744027	0.999956679
ENSG00000260220.6	CCDC187	2.483610551	0.035612745	0.999956679
ENSG00000113430.9	IRX4	2.140360668	0.039222959	0.999956679
ENSG00000166573.5	GALR1	2.066490559	0.033127217	0.999956679
ENSG00000179399.14	GPC5	1.712332177	0.034912216	0.999956679
ENSG00000101447.14	FAM83D	1.675868227	0.00647508	0.999956679
ENSG00000101438.3	SLC32A1	1.646201152	0.037021758	0.999956679
ENSG00000178977.3	LINC00324	1.581503585	0.039300125	0.999956679
ENSG00000235608.1	NKX1-1	1.554607914	0.012615097	0.999956679
ENSG00000220323.4	HIST2H2BD	1.149668445	0.009387136	0.999956679
ENSG00000176236.6	C10orf111	1.104912172	0.04414268	0.999956679
ENSG00000113810.15	SMC4	1.043606297	0.025475074	0.999956679
ENSG00000261716.2	HIST2H2BC	1.039921087	0.017528574	0.999956679
SMA UTX vs SMA miR146a (upregulated in SMA miR-146a)				
Accession number	Genes	log2FoldChange	pvalue	padj
ENSG00000139865.16	TTC6	3.761583522	0.024907596	0.999652218
ENSG00000272140.2	AC022400.5	1.672731479	0.036766722	0.999652218
ENSG00000265972.5	TXNIP	1.275227876	4.54E-09	0.000163732
ENSG00000129534.13	MIS18BP1	1.109852201	0.04001978	0.999652218
ENSG00000175643.9	RMI2	1.043259677	0.036902119	0.999652218
ENSG00000185697.16	MYBL1	1.024490844	0.024593863	0.999652218
Control UTX vs SMA UTX (upregulated in SMA UTX)				
Accession number	Genes	log2FoldChange	pvalue	padj
ENSG00000012817.15	KDM5D	10.99886455	1.24E-13	5.68E-10
ENSG00000233864.7	TTY15	10.95067634	2.41E-14	1.38E-10
ENSG00000131002.11	TXLNGY	10.50886188	1.43E-12	4.09E-09
ENSG00000067048.16	DDX3Y	10.50041921	2.07E-13	7.90E-10
ENSG00000165246.14	NLGN4Y	10.32953175	4.97E-13	1.63E-09
ENSG00000129824.15	RPS4Y1	10.24380928	3.60E-21	8.24E-17
ENSG00000198692.9	EIF1AY	10.21298957	6.22E-12	1.58E-08
ENSG00000183878.15	UTY	9.81060583	4.34E-11	9.04E-08
ENSG00000114374.12	USP9Y	9.18991561	5.51E-18	6.31E-14
ENSG00000154620.5	TMSB4Y	9.112934125	1.32E-09	2.16E-06
ENSG00000241859.6	ANOS2P	8.787913951	4.96E-09	6.69E-06
ENSG00000067646.11	ZFY	8.530243128	3.75E-09	5.37E-06
ENSG00000224318.5	CHL1-AS2	8.466769719	0.044162072	0.999935062
ENSG00000176728.7	TTY14	8.000937836	2.12E-07	0.000231173
ENSG00000099725.14	PRKY	7.651058085	1.28E-07	0.000153899
ENSG00000100351.16	GRAP2	6.419911352	0.000166606	0.097819005
ENSG00000273906.1	AC011297.1	6.396715993	7.14E-05	0.05111123
ENSG00000206159.10	GYG2P1	6.358361387	0.04536056	0.999935062
ENSG00000134121.9	CHL1	6.273318293	0.024428246	0.999935062
ENSG00000233070.1	ZFY-AS1	5.808634863	0.000549137	0.228620768
ENSG00000262539.1	AC005829.2	5.685156129	0.001621935	0.417608527

ENSG00000224116.6	INHBA-AS1	5.681195132	0.001858717	0.46770231
ENSG00000092377.13	TBL1Y	5.521508804	0.00127478	0.371473689
ENSG00000185985.9	SLITRK2	5.403422632	0.00546641	0.828939495
ENSG00000215808.3	LINC01139	5.29082765	0.0019027	0.47356539
ENSG00000230076.1	RPL10P6	5.155978677	0.010474637	0.999935062
ENSG00000240935.6	PLGLA	5.126825579	0.007761522	0.967919048
ENSG00000261613.2	AC093525.6	4.963577552	0.008578133	0.990995906
ENSG00000260197.1	AC010889.1	4.934274733	0.006994839	0.936511246
ENSG00000235590.7	GNAS-AS1	4.680896517	0.004228451	0.711934371
ENSG00000248343.1	AC096576.2	4.643866205	0.007370122	0.939540034
ENSG00000278847.1	AC006157.1	4.582853848	0.016444005	0.999935062
ENSG00000196436.8	NPIP15	4.545905444	0.006103488	0.884542251
ENSG00000236908.2	AC005865.1	4.529650758	0.026978747	0.999935062
ENSG00000248874.5	C5orf17	4.427651772	0.041087568	0.999935062
ENSG00000259199.1	AC022523.1	4.378713067	0.03812922	0.999935062
ENSG00000273248.1	AC010997.4	4.366066099	0.040654819	0.999935062
ENSG00000273657.1	MIR6792	4.35315415	0.03439954	0.999935062
ENSG00000252155.1	RNU6-941P	4.338636703	0.029167323	0.999935062
ENSG00000144355.14	DLX1	4.304113927	0.042115814	0.999935062
ENSG00000259434.1	AC068875.1	4.280401101	0.045362954	0.999935062
ENSG00000138798.11	EGF	4.266741592	0.009726037	0.999935062
ENSG00000229759.1	MRPS18AP1	4.23984479	0.045850879	0.999935062
ENSG00000172799.5	ZBTB8OSP2	4.197068797	0.041583885	0.999935062
ENSG00000281196.1	LINC00934	3.912871742	0.032877643	0.999935062
ENSG00000164756.12	SLC30A8	3.867916785	0.018709178	0.999935062
ENSG00000141668.9	CBLN2	3.787560716	0.008232215	0.99052208
ENSG00000178999.12	AURKB	3.731122856	0.03375602	0.999935062
ENSG00000099715.14	PCDH11Y	3.709949905	2.28E-14	1.38E-10
ENSG00000267774.2	AC010776.2	3.683839623	0.010326323	0.999935062
ENSG00000138136.6	LBX1	3.677310378	0.004392192	0.723542499
ENSG00000197582.5	GPX1P1	3.654350575	0.046913061	0.999935062
ENSG00000236438.7	FAM157A	3.611541766	0.038930064	0.999935062
ENSG00000187140.5	FOXO3	3.565306271	0.006730175	0.935482803
ENSG00000152527.13	PLEKHH2	3.371914024	0.011589774	0.999935062
ENSG00000096395.10	MLN	3.224384997	0.004631065	0.752071834
ENSG00000179399.14	GPC5	3.207758815	0.008971781	0.999935062
ENSG00000258548.5	LINC00645	3.198627038	0.016852537	0.999935062
ENSG00000183287.14	CCBE1	3.16462429	0.000863857	0.302537262
ENSG00000131400.7	NAPSA	2.939315631	0.040590459	0.999935062
ENSG00000230798.5	FOXO3-AS1	2.936960138	0.0167179	0.999935062
ENSG00000227128.4	LBX1-AS1	2.930704688	0.032477312	0.999935062
ENSG00000168952.15	STXBP6	2.881565541	0.026358447	0.999935062
ENSG00000151812.14	SLC35F4	2.75494507	0.033980129	0.999935062
ENSG00000259039.2	AL161804.1	2.746109229	0.033048234	0.999935062
ENSG00000260220.6	CCDC187	2.721229256	0.002470082	0.526535678
ENSG00000171189.17	GRIK1	2.625997253	0.01426247	0.999935062
ENSG00000261502.3	AC040174.1	2.609558986	0.028599011	0.999935062

ENSG00000165966.15	PDZRN4	2.596094754	0.005462044	0.828939495
ENSG00000230435.1	AC004160.2	2.560323365	0.005359199	0.828939495
ENSG00000135824.12	RGS8	2.512818306	0.002122591	0.504019677
ENSG00000019549.11	SNAI2	2.504412327	0.007743524	0.967919048
ENSG00000172243.17	CLEC7A	2.351278492	0.006634573	0.935482803
ENSG00000119715.15	ESRRB	2.277081495	0.044082768	0.999935062
ENSG00000231754.2	AL512380.1	2.245153137	0.036199019	0.999935062
ENSG00000077943.7	ITGA8	2.243945903	0.024314266	0.999935062
ENSG00000254906.1	AC090707.1	2.23322345	0.003410122	0.610038901
ENSG00000250508.1	AP000808.1	2.187671303	0.045594282	0.999935062
ENSG00000116833.13	NR5A2	2.187645635	0.034887128	0.999935062
ENSG00000101463.5	SYNDIG1	2.186707008	0.009989848	0.999935062
ENSG00000272692.1	AC010997.3	2.170658363	0.02950317	0.999935062
ENSG00000246375.2	AC107067.1	2.168692672	0.048606848	0.999935062
ENSG00000101447.14	FAM83D	2.160700648	0.024928397	0.999935062
ENSG00000134258.16	VTCN1	2.130245478	0.002506437	0.526535678
ENSG00000164056.10	SPRY1	2.116608859	0.014461933	0.999935062
ENSG00000178403.3	NEUROG2	2.080479076	0.003209212	0.598232296
ENSG00000259711.1	AC106738.1	2.043995211	0.014532122	0.999935062
ENSG00000276282.1	AC022960.2	2.043971675	0.0367369	0.999935062
ENSG00000163082.9	SGPP2	2.036969811	0.000363274	0.164771187
ENSG00000103449.11	SALL1	1.933434392	0.014741908	0.999935062
ENSG00000227615.1	AP001324.1	1.922396728	0.012060596	0.999935062
ENSG00000164483.16	SAMD3	1.886998006	0.002207697	0.510624604
ENSG00000235996.1	AL136090.1	1.884263047	0.044071503	0.999935062
ENSG00000248632.1	AC106872.5	1.86666721	0.019674945	0.999935062
ENSG00000165973.18	NELL1	1.863453011	0.042829245	0.999935062
ENSG00000169181.12	GSG1L	1.85634257	0.015458002	0.999935062
ENSG00000259363.5	AC090825.1	1.846796669	0.023328776	0.999935062
ENSG00000148948.7	LRRC4C	1.837026966	0.007385676	0.939540034
ENSG00000279565.1	AL121835.2	1.823003338	0.021086866	0.999935062
ENSG00000152818.18	UTRN	1.820414618	0.000222539	0.121326251
ENSG00000100346.17	CACNA1I	1.820380628	0.026548292	0.999935062
ENSG00000180875.4	GREM2	1.805562854	0.028518877	0.999935062
ENSG00000214401.4	KANSL1-AS1	1.76902466	0.039641738	0.999935062
ENSG00000109861.15	CTSC	1.736575612	0.034247521	0.999935062
ENSG00000236333.3	TRHDE-AS1	1.709136439	0.014937854	0.999935062
ENSG00000189337.16	KAZN	1.698697194	0.031263127	0.999935062
ENSG00000237457.6	LINC01351	1.6927666	0.040774299	0.999935062
ENSG00000264843.1	AP001180.4	1.66954854	0.014833047	0.999935062
ENSG00000176842.14	IRX5	1.667456664	0.048861792	0.999935062
ENSG00000210112.1	MT-TM	1.649520187	0.017994139	0.999935062
ENSG00000226964.1	RHEBP2	1.633427956	0.045552134	0.999935062
ENSG00000279675.1	AC080100.1	1.631775313	0.007017928	0.936511246
ENSG00000175147.12	TMEM51-AS1	1.629008882	0.027297779	0.999935062
ENSG00000120162.9	MOB3B	1.624768555	0.031011789	0.999935062
ENSG00000285095.1	AC025887.2	1.605949687	0.045571324	0.999935062

ENSG00000263970.1	AP001094.1	1.601430919	0.028021221	0.999935062
ENSG00000105991.8	HOXA1	1.568760331	0.021658292	0.999935062
ENSG00000182022.17	CHST15	1.555881106	0.033258014	0.999935062
ENSG00000282375.1	AC100797.4	1.539030826	0.006740967	0.935482803
ENSG00000225811.1	AL354771.1	1.493491292	0.016207603	0.999935062
ENSG00000188517.15	COL25A1	1.490202805	0.000803538	0.294664358
ENSG00000147869.4	CER1	1.487947569	0.048064848	0.999935062
ENSG00000111913.18	RIPOR2	1.486407303	0.030966828	0.999935062
ENSG00000171246.5	NPTX1	1.470391621	0.028650691	0.999935062
ENSG00000008311.14	AASS	1.464404557	0.006601069	0.935482803
ENSG00000104313.18	EYA1	1.443704757	0.010481986	0.999935062
ENSG00000101443.17	WFDC2	1.441339189	0.018819324	0.999935062
ENSG00000082497.11	SERTAD4	1.432875836	0.040919755	0.999935062
ENSG00000196353.11	CPNE4	1.430849988	0.03925162	0.999935062
ENSG00000162949.16	CAPN13	1.425917523	0.044291774	0.999935062
ENSG00000153976.2	HS3ST3A1	1.420590546	0.006949899	0.936511246
ENSG00000187720.14	THSD4	1.419869968	0.013901438	0.999935062
ENSG00000231672.6	DIRC3	1.382741165	0.024600553	0.999935062
ENSG00000243715.1	CACNA2D3-AS1	1.37234521	0.008116962	0.988628662
ENSG00000240207.6	AC080013.1	1.368092533	0.005164728	0.804502993
ENSG00000123454.11	DBH	1.363402195	0.002464733	0.526535678
ENSG00000197565.15	COL4A6	1.355967217	0.011542281	0.999935062
ENSG00000132205.10	EMILIN2	1.353777226	0.03034956	0.999935062
ENSG00000277268.1	LHX1-DT	1.34630577	0.018092958	0.999935062
ENSG00000255164.1	AF235103.1	1.335755209	0.018553339	0.999935062
ENSG00000274512.5	TBC1D3L	1.334620679	0.04151577	0.999935062
ENSG00000185774.15	KCNIP4	1.329408948	0.00116347	0.364946953
ENSG00000260641.1	AC114811.2	1.328652892	0.007052531	0.936511246
ENSG00000146276.11	GABRR1	1.323975752	0.002982784	0.58007687
ENSG00000176641.10	RNF152	1.310417708	0.000621458	0.249651598
ENSG00000138670.17	RASGEF1B	1.308059444	0.002135117	0.504019677
ENSG00000187398.11	LUZP2	1.307065342	0.001013097	0.334416805
ENSG00000275327.1	AL354950.2	1.301173095	0.008383615	0.990995906
ENSG00000259863.1	SH3RF3-AS1	1.295788452	0.041838392	0.999935062
ENSG00000270087.5	ZNF503	1.291567761	0.03253356	0.999935062
ENSG00000182601.6	HS3ST4	1.274001715	0.008262281	0.99052208
ENSG00000139910.19	NOVA1	1.245446931	0.00260144	0.535007881
ENSG00000170703.15	TTLL6	1.239375651	0.043939364	0.999935062
ENSG00000250241.5	AC105383.1	1.236355091	0.01555511	0.999935062
ENSG00000144821.9	MYH15	1.229711465	0.016880059	0.999935062
ENSG00000280135.1	AL096816.1	1.227688189	0.037452953	0.999935062
ENSG00000196482.16	ESRRG	1.223603993	0.003711677	0.648778432
ENSG00000157445.14	CACNA2D3	1.223004997	0.001591498	0.417608527
ENSG00000182667.14	NTM	1.20605924	0.002568389	0.534645256
ENSG00000165443.11	PHYHIP1L	1.202682699	0.003162662	0.598232296
ENSG00000196542.8	SPTSSB	1.201069459	0.026071673	0.999935062
ENSG00000109819.8	PPARGC1A	1.199152899	0.005111397	0.801649134

ENSG00000261308.2	FIGNL2	1.198975716	0.007239169	0.936511246
ENSG00000225697.12	SLC26A6	1.190984814	0.005968395	0.880292135
ENSG00000113389.15	NPR3	1.184662057	0.000546613	0.228620768
ENSG00000147174.11	GCNA	1.177456299	0.046879325	0.999935062
ENSG00000164082.14	GRM2	1.162695773	0.012531644	0.999935062
ENSG00000270059.1	AC121493.1	1.160044652	0.028838176	0.999935062
ENSG00000284299.1	AL590132.1	1.15674972	0.043493527	0.999935062
ENSG00000175928.5	LRRN1	1.152788078	0.009034696	0.999935062
ENSG00000258052.1	AC025263.2	1.145661561	0.035152675	0.999935062
ENSG00000127328.21	RAB3IP	1.134519798	0.011872669	0.999935062
ENSG00000041515.15	MYO16	1.134047543	0.002616861	0.535007881
ENSG00000120075.5	HOXB5	1.129625207	0.004872055	0.780142115
ENSG00000204524.6	ZNF805	1.120421794	0.022375376	0.999935062
ENSG00000125398.6	SOX9	1.119743367	0.011654189	0.999935062
ENSG00000174498.13	IGDCC3	1.115733113	0.0104251	0.999935062
ENSG00000089169.14	RPH3A	1.108734796	0.003389571	0.610038901
ENSG00000013573.16	DDX11	1.106489203	0.008467077	0.990995906
ENSG00000276644.4	DACH1	1.103526991	0.019394346	0.999935062
ENSG00000172260.14	NEGR1	1.094132645	0.00574796	0.86024051
ENSG00000238083.7	LRR37A2	1.093048555	0.027116973	0.999935062
ENSG00000187416.11	LHFPL3	1.087138045	0.020720779	0.999935062
ENSG00000272973.1	AP000350.5	1.078137947	0.031376252	0.999935062
ENSG00000172985.10	SH3RF3	1.068486203	0.010681727	0.999935062
ENSG00000235026.5	DPP10-AS1	1.065418601	0.042365262	0.999935062
ENSG00000272078.1	AL139423.1	1.059718714	0.009607806	0.999935062
ENSG00000110328.5	GALNT18	1.059486106	0.037302453	0.999935062
ENSG00000176381.5	PRR18	1.05905186	0.030251718	0.999935062
ENSG00000250761.2	AC093305.1	1.055085127	0.022834748	0.999935062
ENSG00000106278.11	PTPRZ1	1.050184734	0.026859605	0.999935062
ENSG00000197576.13	HOXA4	1.049722676	0.011227112	0.999935062
ENSG00000105287.12	PRKD2	1.048331842	0.014438555	0.999935062
ENSG00000118432.12	CNR1	1.045654266	0.01317555	0.999935062
ENSG00000279726.1	AC005609.5	1.044580802	0.026915378	0.999935062
ENSG00000121005.8	CRISPLD1	1.04105209	0.00720093	0.936511246
ENSG00000139915.19	MDGA2	1.036632788	0.018622142	0.999935062
ENSG00000132821.11	VSTM2L	1.020705521	0.017341786	0.999935062
ENSG00000162490.6	DRAXIN	1.015638463	0.004089047	0.693562906
ENSG00000102384.13	CENPI	1.009960231	0.021297582	0.999935062
ENSG00000130940.14	CASZ1	1.00415335	0.009195705	0.999935062
Control UTX vs Control miR-146a (downregulated in control miR-146a)				
Accession number	Genes	log2FoldChange	pvalue	padj
ENSG00000163017.13	ACTG2	-1.942322858	1.08E-05	0.214441393
ENSG00000101542.9	CDH20	-2.033044669	1.57E-05	0.214441393
ENSG00000130829.17	DUSP9	-2.149476207	1.94E-05	0.214441393
ENSG00000139874.5	SSTR1	-1.420857148	3.72E-05	0.256351553
ENSG00000186340.15	THBS2	-1.292578731	3.86E-05	0.256351553

ENSG00000121769.7	FABP3	-1.223623345	6.27E-05	0.347479702
ENSG00000274956.2	NKAIN3-IT1	-1.218698724	9.77E-05	0.463659735
ENSG00000135312.6	HTR1B	-1.468948122	0.000128525	0.469547214
ENSG00000179520.10	SLC17A8	-1.419872465	0.000147554	0.469547214
ENSG00000250305.8	TRMT9B	-1.236466729	0.000153429	0.469547214
ENSG00000174403.15	MIR1-1HG-AS1	-1.309983026	0.000155451	0.469547214
ENSG00000168546.10	GFRA2	-1.138299515	0.000213018	0.589812168
ENSG00000103335.22	PIEZO1	-1.379075635	0.000277955	0.705235043
ENSG00000178695.5	KCTD12	-1.041833925	0.000297156	0.705235043
ENSG00000017427.16	IGF1	-2.025482121	0.00033199	0.709290568
ENSG00000211445.11	GPX3	-1.050806825	0.000342855	0.709290568
ENSG00000260121.1	AC138028.4	-1.817070451	0.000362907	0.709290568
ENSG00000041982.15	TNC	-1.21695014	0.000431327	0.743553689
ENSG00000178562.17	CD28	-2.468872723	0.000435001	0.743553689
ENSG00000198785.4	GRIN3A	-1.075936921	0.000447573	0.743553689
ENSG00000125931.10	CITED1	-1.178144361	0.000475311	0.752032838
ENSG00000198400.11	NTRK1	-2.289696219	0.000633131	0.914626827
ENSG00000186642.15	PDE2A	-1.324707982	0.000662363	0.916985899
ENSG00000254656.2	RTL1	-1.670851185	0.000788052	0.999956679
ENSG00000164683.16	HEY1	-1.031147505	0.000836759	0.999956679
ENSG00000111859.16	NEDD9	-1.395965251	0.000915914	0.999956679
ENSG00000164106.7	SCRG1	-1.263161712	0.000922331	0.999956679
ENSG00000095397.13	WHRN	-1.018010942	0.000925373	0.999956679
ENSG00000285744.1	AC083837.2	-1.583137827	0.001020997	0.999956679
ENSG00000125510.15	OPRL1	-1.005697891	0.001152864	0.999956679
ENSG00000178726.6	THBD	-1.384167483	0.001159419	0.999956679
ENSG00000134207.16	SYT6	-1.132764953	0.001231154	0.999956679
ENSG00000181634.7	TNFSF15	-2.572880063	0.001395266	0.999956679
ENSG00000281344.1	HELLPAR	-1.720817384	0.001497005	0.999956679
ENSG00000165029.15	ABCA1	-1.183797947	0.001646448	0.999956679
ENSG00000198598.6	MMP17	-1.052654793	0.001692833	0.999956679
ENSG00000114204.14	SERPINI2	-3.042138096	0.002456333	0.999956679
ENSG00000169083.16	AR	-1.338023598	0.002729661	0.999956679
ENSG00000180176.14	TH	-1.566968824	0.002845856	0.999956679
ENSG00000152766.5	ANKRD22	-3.440654476	0.002873775	0.999956679
ENSG00000162511.7	LAPTM5	-1.690740135	0.002938038	0.999956679
ENSG00000162645.12	GBP2	-1.907755564	0.003084332	0.999956679
ENSG00000134363.11	FST	-2.772883875	0.003272824	0.999956679
ENSG00000185760.15	KCNQ5	-2.082527213	0.00343764	0.999956679
ENSG00000183036.10	PCP4	-1.637221617	0.003891767	0.999956679
ENSG00000165025.14	SYK	-1.489350331	0.003894102	0.999956679
ENSG00000185742.6	C11orf87	-1.019381172	0.004117929	0.999956679
ENSG00000148175.12	STOM	-1.05726757	0.004567643	0.999956679
ENSG00000163565.18	IFI16	-1.381070823	0.004628536	0.999956679
ENSG00000169676.5	DRD5	-1.538420066	0.005292695	0.999956679
ENSG00000149591.16	TAGLN	-1.032705018	0.005465793	0.999956679
ENSG00000187688.14	TRPV2	-1.471747678	0.005532605	0.999956679

ENSG00000142102.15	PGGHG	-1.180598206	0.00566931	0.999956679
ENSG00000196739.14	COL27A1	-1.841609302	0.005878967	0.999956679
ENSG00000204110.6	LINC02520	-1.802221574	0.005935456	0.999956679
ENSG00000105509.10	HAS1	-1.401532701	0.006044196	0.999956679
ENSG00000189221.9	MAOA	-1.140194699	0.006111029	0.999956679
ENSG00000148677.6	ANKRD1	-1.744592067	0.006186524	0.999956679
ENSG00000119681.11	LTBP2	-1.472118912	0.006375201	0.999956679
ENSG00000066248.14	NGEF	-1.343945315	0.006554222	0.999956679
ENSG00000087116.15	ADAMTS2	-1.215413475	0.006915526	0.999956679
ENSG00000130176.7	CNN1	-1.193375508	0.006982054	0.999956679
ENSG00000165272.15	AQP3	-2.102158562	0.007062107	0.999956679
ENSG00000145681.10	HAPLN1	-1.779302108	0.007362945	0.999956679
ENSG00000225614.2	ZNF469	-1.659173982	0.007737391	0.999956679
ENSG00000141744.3	PNMT	-1.175015471	0.008783448	0.999956679
ENSG00000118985.15	ELL2	-1.120301665	0.008895263	0.999956679
ENSG00000138639.17	ARHGAP24	-1.406974309	0.008974876	0.999956679
ENSG00000120937.8	NPPB	-1.366311071	0.00908017	0.999956679
ENSG00000108932.11	SLC16A6	-1.018007162	0.009141863	0.999956679
ENSG00000135218.18	CD36	-1.924299276	0.009425822	0.999956679
ENSG00000131724.10	IL13RA1	-1.117911596	0.009749475	0.999956679
ENSG00000225216.6	AC007362.1	-1.046718287	0.010033717	0.999956679
ENSG00000185942.11	NKAIN3	-1.166139338	0.010597787	0.999956679
ENSG00000112562.18	SMOC2	-1.295297824	0.010604807	0.999956679
ENSG00000196083.9	IL1RAP	-1.038327092	0.010958212	0.999956679
ENSG00000101335.9	MYL9	-1.125352032	0.011252716	0.999956679
ENSG00000166603.5	MC4R	-4.217579467	0.011368507	0.999956679
ENSG00000141448.8	GATA6	-1.557468714	0.011980157	0.999956679
ENSG00000259583.2	AC015712.2	-1.794128519	0.012149519	0.999956679
ENSG00000179603.17	GRM8	-1.145031793	0.012437574	0.999956679
ENSG00000140853.15	NLRC5	-2.020198476	0.012628125	0.999956679
ENSG00000184557.4	SOCS3	-1.010951257	0.012981745	0.999956679
ENSG00000069482.6	GAL	-1.016367649	0.013014912	0.999956679
ENSG00000086696.10	HSD17B2	-2.604773148	0.013390969	0.999956679
ENSG00000157570.11	TSPAN18	-1.029905556	0.013537881	0.999956679
ENSG00000121764.11	HCRTR1	-1.018869512	0.0135983	0.999956679
ENSG00000162433.14	AK4	-1.000128069	0.014024557	0.999956679
ENSG00000184254.16	ALDH1A3	-1.760115022	0.014561689	0.999956679
ENSG00000115363.13	EVA1A	-1.149243464	0.014631071	0.999956679
ENSG00000128271.21	ADORA2A	-1.081510741	0.015679412	0.999956679
ENSG00000156219.16	ART3	-1.627210963	0.016033079	0.999956679
ENSG00000163840.9	DTX3L	-1.332568037	0.016047838	0.999956679
ENSG00000271824.1	SMIM32	-1.025346027	0.01669739	0.999956679
ENSG00000171617.13	ENC1	-1.550581056	0.017203427	0.999956679
ENSG00000147434.8	CHRNA6	-1.708693282	0.017486203	0.999956679
ENSG00000187699.10	C2orf88	-1.497099848	0.018382998	0.999956679
ENSG00000138772.12	ANXA3	-1.181815148	0.019054787	0.999956679
ENSG00000109205.16	ODAM	-4.073028335	0.019078101	0.999956679

ENSG00000106366.8	SERPINE1	-1.810437299	0.020147764	0.999956679
ENSG00000169836.4	TACR3	-1.716256285	0.021137235	0.999956679
ENSG00000259207.7	ITGB3	-1.35747461	0.02229567	0.999956679
ENSG00000140057.8	AK7	-1.318074609	0.022363125	0.999956679
ENSG00000185155.11	MIXL1	-1.457241842	0.022691633	0.999956679
ENSG00000198732.10	SMOC1	-1.298415498	0.023308666	0.999956679
ENSG00000176170.13	SPHK1	-1.22731751	0.023500816	0.999956679
ENSG00000164251.4	F2RL1	-1.338317166	0.024459938	0.999956679
ENSG00000180758.11	GPR157	-1.093664199	0.024731	0.999956679
ENSG00000184156.16	KCNQ3	-1.57699829	0.024740928	0.999956679
ENSG00000267272.5	LINC01140	-1.864290936	0.02585527	0.999956679
ENSG00000141682.11	PMAIP1	-1.504022203	0.026283998	0.999956679
ENSG00000118322.13	ATP10B	-3.490951015	0.027183346	0.999956679
ENSG00000175445.15	LPL	-2.616894987	0.027249113	0.999956679
ENSG00000113083.13	LOX	-1.14456434	0.027267056	0.999956679
ENSG00000137198.9	GMPR	-1.302638795	0.027339949	0.999956679
ENSG00000119630.13	PGF	-1.230931033	0.030111628	0.999956679
ENSG00000261150.2	EPPK1	-1.121221587	0.030329678	0.999956679
ENSG00000235568.6	NFAM1	-1.475325982	0.030774394	0.999956679
ENSG00000205856.3	C22orf42	-1.281407426	0.030826464	0.999956679
ENSG00000250899.3	AC125807.2	-1.046406124	0.031241967	0.999956679
ENSG00000171759.9	PAH	-1.506219434	0.032452203	0.999956679
ENSG00000072858.10	SIDT1	-1.669539954	0.033995264	0.999956679
ENSG00000099994.10	SUSD2	-1.088992643	0.034137171	0.999956679
ENSG00000137831.14	UACA	-1.152697936	0.034209452	0.999956679
ENSG00000133636.10	NTS	-2.057686253	0.0342156	0.999956679
ENSG00000204950.3	LRRC10B	-1.407298514	0.034919681	0.999956679
ENSG00000144810.15	COL8A1	-1.291180861	0.035287528	0.999956679
ENSG00000272114.1	AL136131.3	-1.164026503	0.036200974	0.999956679
ENSG00000278709.1	NKILA	-1.020037113	0.036535218	0.999956679
ENSG00000152208.12	GRID2	-1.218859898	0.036818012	0.999956679
ENSG00000174776.11	WDR49	-2.124881428	0.037120001	0.999956679
ENSG00000138496.16	PARP9	-1.375781153	0.038736495	0.999956679
ENSG00000120708.16	TGFBI	-1.026273486	0.039119052	0.999956679
ENSG00000145451.12	GLRA3	-1.067490436	0.040200363	0.999956679
ENSG00000253931.1	AC105118.1	-1.449708529	0.040383969	0.999956679
ENSG00000259753.1	AC068234.1	-1.295505917	0.040703	0.999956679
ENSG00000152049.6	KCNE4	-1.66165327	0.041185612	0.999956679
ENSG00000174792.10	ODAPH	-1.178267876	0.04182905	0.999956679
ENSG00000049540.16	ELN	-3.425336483	0.041964637	0.999956679
ENSG00000111452.12	ADGRD1	-1.28733896	0.042095838	0.999956679
ENSG00000186867.10	QRFRP	-4.839496416	0.043157561	0.999956679
ENSG00000181085.14	MAPK15	-1.197772629	0.043694134	0.999956679
ENSG00000135744.7	AGT	-1.814935014	0.043897076	0.999956679
ENSG00000187889.12	FYB2	-4.234248802	0.044146292	0.999956679
ENSG00000173077.15		1-Dec	0.046385448	0.999956679
ENSG00000180440.3	SERTM1	-1.646951853	0.046617949	0.999956679

ENSG00000196990.8	FAM163B	-1.098494257	0.046870282	0.999956679
ENSG00000197859.9	ADAMTSL2	-1.523000378	0.0471148058	0.999956679
ENSG00000122641.10	INHBA	-1.505239351	0.048662608	0.999956679
SMA UTX vs SMA miR-146a (downregulated in SMA miR-146a)				
Accession number	Genes	log2FoldChange	pvalue	padj
ENSG00000184454.6	NCMAP	-4.865595991	0.001578251	0.999652218
ENSG00000232369.1	PPIAP35	-4.289745759	0.012046206	0.999652218
ENSG00000112041.12	TULP1	-3.743554279	0.02972894	0.999652218
ENSG00000228079.2	AC012368.2	-3.655575354	0.03099934	0.999652218
ENSG00000144355.14	DLX1	-3.638860661	0.011821969	0.999652218
ENSG00000229896.2	AL157373.2	-3.538476029	0.031426609	0.999652218
ENSG00000258256.1	AC011773.3	-3.538476029	0.031426609	0.999652218
ENSG00000162391.11	FAM151A	-3.394332366	0.041911421	0.999652218
ENSG00000232118.2	BACH1-AS1	-3.035218121	0.046422866	0.999652218
ENSG00000207942.2	MIR136	-2.923210989	0.011685432	0.999652218
ENSG00000236838.2	AC090617.2	-2.824515067	0.040585025	0.999652218
ENSG00000278740.1	AC005332.7	-2.816269088	0.039222681	0.999652218
ENSG00000198829.6	SUCNR1	-2.715870342	0.005043322	0.999652218
ENSG00000236617.2	AC127070.1	-2.649463118	0.042686497	0.999652218
ENSG00000152214.13	RIT2	-2.636973718	0.048282788	0.999652218
ENSG00000230328.2	AL359893.1	-2.550661612	0.007213771	0.999652218
ENSG00000166819.11	PLIN1	-2.492269309	0.00496528	0.999652218
ENSG00000264468.1	MIR4520-1	-2.300583376	0.029912436	0.999652218
ENSG00000144331.19	ZNF385B	-2.289133774	0.000508645	0.999652218
ENSG00000138316.10	ADAMTS14	-2.242665641	0.042216839	0.999652218
ENSG00000197465.13	GYPE	-2.200746225	0.011364079	0.999652218
ENSG00000196136.17	SERPINA3	-2.190524335	0.048899346	0.999652218
ENSG00000074966.10	TXK	-2.183125299	0.018858299	0.999652218
ENSG00000173338.12	KCNK7	-2.151543123	0.033392771	0.999652218
ENSG00000178562.17	CD28	-2.128060979	0.000255092	0.704733416
ENSG00000166292.11	TMEM100	-2.080896212	0.003200888	0.999652218
ENSG00000249937.6	LINC02223	-2.06304465	0.029831223	0.999652218
ENSG00000106631.8	MYL7	-2.040165665	0.041243972	0.999652218
ENSG00000114204.14	SERPINI2	-2.038739566	0.018291931	0.999652218
ENSG00000038295.7	TLL1	-1.964389934	0.013220051	0.999652218
ENSG00000130433.7	CACNG6	-1.896302884	0.048747181	0.999652218
ENSG00000248323.6	LUCAT1	-1.887286405	0.025330143	0.999652218
ENSG00000235597.1	LINC01102	-1.877977566	0.03987313	0.999652218
ENSG00000284118.1	MIR4707	-1.877450867	0.027396119	0.999652218
ENSG00000101306.10	MYLK2	-1.840072105	0.024453814	0.999652218
ENSG00000181634.7	TNFSF15	-1.728599057	0.048000423	0.999652218
ENSG00000110799.13	VWF	-1.722494622	0.016922735	0.999652218
ENSG00000100078.3	PLA2G3	-1.708743398	0.005304718	0.999652218
ENSG00000262294.1	AC129507.2	-1.694287775	0.002823825	0.999652218
ENSG00000172243.17	CLEC7A	-1.667699541	0.003585957	0.999652218
ENSG00000138798.11	EGF	-1.665290544	0.015753622	0.999652218

ENSG00000162511.7	LAPTM5	-1.622022781	8.96E-05	0.403423501
ENSG00000069431.11	ABCC9	-1.607307406	0.006427869	0.999652218
ENSG00000283857.1	MIR1247	-1.598981965	0.049402863	0.999652218
ENSG00000197921.5	HES5	-1.565564727	0.02687692	0.999652218
ENSG00000139329.4	LUM	-1.561442831	0.030951645	0.999652218
ENSG00000136160.15	EDNRB	-1.551893261	0.032012998	0.999652218
ENSG00000179520.10	SLC17A8	-1.551053086	9.91E-06	0.07139637
ENSG00000166670.9	MMP10	-1.550767375	0.018197055	0.999652218
ENSG00000065361.15	ERBB3	-1.512105956	0.030016759	0.999652218
ENSG00000196611.4	MMP1	-1.501155363	1.69E-05	0.101449354
ENSG00000183036.10	PCP4	-1.498331822	0.007022994	0.999652218
ENSG00000159674.11	SPON2	-1.487550385	0.042906376	0.999652218
ENSG00000150556.16	LYPD6B	-1.479518008	0.031562014	0.999652218
ENSG00000072858.10	SIDT1	-1.477590385	0.013216187	0.999652218
ENSG00000170044.8	ZPLD1	-1.475687942	0.026584075	0.999652218
ENSG00000175445.15	LPL	-1.471685698	0.043279492	0.999652218
ENSG00000284265.1	MIR4683	-1.468752449	0.044659989	0.999652218
ENSG00000145451.12	GLRA3	-1.45138205	5.57E-06	0.050161367
ENSG00000120341.18	SEC16B	-1.438686877	0.040117916	0.999652218
ENSG00000227098.1	AC073636.1	-1.421061053	0.037074909	0.999652218
ENSG00000234899.9	SOX9-AS1	-1.420630867	0.027722859	0.999652218
ENSG00000169836.4	TACR3	-1.419568437	0.000242124	0.704733416
ENSG00000251468.2	AC135352.1	-1.416726258	0.027346129	0.999652218
ENSG00000168594.15	ADAM29	-1.404169303	0.042272588	0.999652218
ENSG00000152049.6	KCNE4	-1.380856017	0.00746666	0.999652218
ENSG00000147408.14	CSGALNACT1	-1.357562978	0.037919738	0.999652218
ENSG00000154188.9	ANGPT1	-1.352897022	0.000168979	0.609000961
ENSG00000133454.15	MYO18B	-1.345368041	0.023123023	0.999652218
ENSG00000204277.1	LINC01993	-1.306198664	0.002214173	0.999652218
ENSG00000264515.5	AC011474.1	-1.30385732	0.008354498	0.999652218
ENSG00000102384.13	CENPI	-1.287254836	1.97E-05	0.101449354
ENSG00000187699.10	C2orf88	-1.284835876	0.01243816	0.999652218
ENSG00000189410.11	SH2D5	-1.280817775	2.84E-06	0.034095694
ENSG00000099958.14	DERL3	-1.263504839	0.00013938	0.558139678
ENSG00000174343.5	CHRNA9	-1.262717169	0.013242404	0.999652218
ENSG00000183578.7	TNFAIP8L3	-1.253463879	0.000375093	0.901223431
ENSG00000261150.2	EPPK1	-1.245110107	0.005286663	0.999652218
ENSG00000067182.7	TNFRSF1A	-1.242518268	1.51E-07	0.002723473
ENSG00000147509.13	RGS20	-1.231380508	0.01995221	0.999652218
ENSG00000198400.11	NTRK1	-1.212494834	0.0067457	0.999652218
ENSG00000285758.1	AC036214.4	-1.211370143	0.031934927	0.999652218
ENSG00000233901.5	LINC01503	-1.203565288	0.028603338	0.999652218
ENSG00000163017.13	ACTG2	-1.200602719	0.001704553	0.999652218
ENSG00000165029.15	ABCA1	-1.177984236	0.000474062	0.999652218
ENSG00000170442.11	KRT86	-1.16098177	0.037191966	0.999652218
ENSG00000140682.18	TGFB11	-1.149073524	0.001044376	0.999652218
ENSG00000115232.13	ITGA4	-1.140090935	0.002180276	0.999652218

ENSG00000069482.6	GAL	-1.136380954	0.007299594	0.999652218
ENSG00000122641.10	INHBA	-1.134737632	0.02204025	0.999652218
ENSG00000121769.7	FABP3	-1.132050319	0.0002027	0.664119368
ENSG00000259546.1	AC027808.1	-1.128798181	0.029179851	0.999652218
ENSG00000285744.1	AC083837.2	-1.121216329	0.012199484	0.999652218
ENSG00000152760.9	TCTEX1D1	-1.120986122	0.022395184	0.999652218
ENSG00000082293.12	COL19A1	-1.116707273	0.037949797	0.999652218
ENSG00000185760.15	KCNQ5	-1.111911311	0.030219898	0.999652218
ENSG00000148677.6	ANKRD1	-1.095364315	0.008958452	0.999652218
ENSG00000254510.1	AP001107.5	-1.094411961	0.008083931	0.999652218
ENSG00000260121.1	AC138028.4	-1.093150607	0.023426642	0.999652218
ENSG00000147869.4	CER1	-1.088967216	0.038064246	0.999652218
ENSG00000248801.6	C8orf34-AS1	-1.073941435	0.008701288	0.999652218
ENSG00000163638.13	ADAMTS9	-1.073375909	0.019817522	0.999652218
ENSG00000075429.8	CACNG5	-1.071003937	0.016919059	0.999652218
ENSG00000156140.9	ADAMTS3	-1.069564539	0.015312721	0.999652218
ENSG00000185664.14	PMEL	-1.063975013	0.002477637	0.999652218
ENSG00000142102.15	PGGHG	-1.059388967	0.003253718	0.999652218
ENSG00000087076.8	HSD17B14	-1.056324446	0.002472015	0.999652218
ENSG00000198753.11	PLXNB3	-1.048026637	0.022636331	0.999652218
ENSG00000261320.1	AC009061.1	-1.047861793	0.009649833	0.999652218
ENSG00000204110.6	LINC02520	-1.046844847	0.020877021	0.999652218
ENSG00000118985.15	ELL2	-1.028967124	0.002203357	0.999652218
ENSG00000144802.11	NFKBIZ	-1.024129498	0.009926634	0.999652218
ENSG00000228824.6	MIR4500HG	-1.01529295	0.027421292	0.999652218
ENSG00000133121.20	STARD13	-1.014032938	0.010631413	0.999652218
ENSG00000160883.10	HK3	-1.008831967	0.038584122	0.999652218
Control UTX vs SMA UTX (downregulated in SMA UTX)				
Accession number	Genes	log2FoldChange	pvalue	padj
ENSG00000176769.9	TCERG1L	-24.08927147	3.58E-09	5.37E-06
ENSG00000147724.11	FAM135B	-8.761797158	0.031847923	0.999935062
ENSG00000226278.1	PSPHP1	-7.7816499	5.08E-10	8.95E-07
ENSG00000169436.16	COL22A1	-7.000320501	0.031684522	0.999935062
ENSG00000229807.11	XIST	-5.945399206	0.01690099	0.999935062
ENSG00000250284.2	AC109439.2	-5.829507187	7.27E-06	0.006289051
ENSG00000166959.7	MS4A8	-5.616041257	0.002382509	0.521994636
ENSG00000172062.16	SMN1	-5.535447451	7.91E-07	0.000787172
ENSG00000204894.4	AC104692.1	-5.462548459	0.002989303	0.58007687
ENSG00000231589.1	AC009110.1	-5.416631853	0.001476047	0.402363267
ENSG00000131096.10	PYY	-5.397420991	0.011596257	0.999935062
ENSG00000159450.12	TCHH	-5.3474571	0.004748451	0.765704427
ENSG00000235254.3	TMEM185AP1	-5.327857558	0.001461345	0.402363267
ENSG00000185290.3	NUPR2	-5.321094363	0.005451565	0.828939495
ENSG00000133710.15	SPINK5	-5.226235238	3.31E-07	0.000344209
ENSG00000270405.1	AC104692.2	-5.146622762	0.009552226	1
ENSG00000285644.1	AC108448.3	-4.894554498	0.000733903	0.278163783

ENSG00000270641.1	TSIX	-4.867777642	0.002189527	0.510624604
ENSG00000075643.5	MOCOS	-4.67692949	0.039666556	1
ENSG00000215262.7	KCNU1	-4.537222891	0.047340069	0.999935062
ENSG00000259051.1	HNRNPUP1	-4.444452239	0.018735107	0.999935062
ENSG00000138161.13	CUZD1	-4.414111132	0.023362457	0.999935062
ENSG00000143768.12	LEFTY2	-4.280408415	0.013163044	0.999935062
ENSG00000146001.5	PCDHB18P	-4.214942396	1.02E-05	0.008355266
ENSG00000275266.1	RF01972	-4.08825605	0.000116055	0.073817708
ENSG00000110077.14	MS4A6A	-4.058209805	0.042208988	1
ENSG00000250982.2	GAPDHP35	-3.978842006	8.25E-09	1.05E-05
ENSG00000272983.1	AL117339.4	-3.953274828	0.020068814	0.999935062
ENSG00000258425.1	AC013451.1	-3.868968934	0.035299578	0.999935062
ENSG00000217643.1	PTGES3P2	-3.825943672	0.032279346	0.999935062
ENSG00000111704.10	NANOG	-3.806554209	0.023190029	0.999935062
ENSG00000162595.6	DIRAS3	-3.718845298	0.008815324	0.997704562
ENSG00000130600.18	H19	-3.650840986	0.003065307	0.587697557
ENSG00000227827.3	AC138969.1	-3.648853063	0.003246411	0.599486478
ENSG00000268297.1	CLEC4GP1	-3.608380444	0.000993269	0.334416805
ENSG00000284727.1	AC116562.4	-3.567073489	0.016078507	0.999935062
ENSG00000160321.14	ZNF208	-3.563968796	0.002393634	0.521994636
ENSG00000269994.2	AL513318.2	-3.537240147	1.36E-05	0.010719534
ENSG00000196109.7	ZNF676	-3.535915402	0.041147518	0.999935062
ENSG00000281566.3	AL157778.1	-3.53545109	1.74E-11	3.98E-08
ENSG00000134817.10	APLNR	-3.5128014	0.029387951	0.999935062
ENSG00000132622.10	HSPA12B	-3.435842941	0.00272392	0.551967437
ENSG00000153347.9	FAM81B	-3.309437742	0.023861729	0.999935062
ENSG00000169248.12	CXCL11	-3.30001832	0.022610154	0.999935062
ENSG00000004848.7	ARX	-3.173856274	7.14E-06	0.006289051
ENSG00000118322.13	ATP10B	-3.151315714	0.028990152	0.999935062
ENSG00000262096.2	PCDHB19P	-3.130125262	0.014117439	0.999935062
ENSG00000099251.14	HSD17B7P2	-3.117717297	0.000634597	0.250534499
ENSG00000224743.6	TEX26-AS1	-3.11758184	0.047913753	0.999935062
ENSG00000102802.9	MEDAG	-3.004099037	0.023217311	0.999935062
ENSG00000115085.13	ZAP70	-2.968773438	0.036074467	0.999935062
ENSG00000077274.8	CAPN6	-2.865126292	0.001787394	0.454752724
ENSG00000181634.7	TNFSF15	-2.863858216	0.000265834	0.135268373
ENSG00000026508.18	CD44	-2.842275737	0.014174833	0.999935062
ENSG00000221963.5	APOL6	-2.743665627	0.009222827	0.999935062
ENSG00000228232.1	GAPDHP1	-2.698166617	2.31E-10	4.41E-07
ENSG00000163347.5	CLDN1	-2.618747185	0.030668576	0.999935062
ENSG00000175445.15	LPL	-2.588983111	0.044130029	0.999935062
ENSG00000017427.16	IGF1	-2.565735607	0.018701635	0.999935062
ENSG00000255085.8	AF186192.2	-2.54554431	3.11E-06	0.002967766
ENSG00000107187.16	LHX3	-2.540208332	0.045171672	0.999935062
ENSG00000197134.11	ZNF257	-2.530063822	0.006099133	0.884542251
ENSG00000006128.11	TAC1	-2.493225121	0.044159438	0.999935062
ENSG00000180229.12	HERC2P3	-2.423443208	0.00993345	0.999935062

ENSG00000128617.2	OPN1SW	-2.421800298	8.73E-05	0.060596791
ENSG00000255622.3	PCDHB17P	-2.421413795	0.045328011	0.999935062
ENSG00000164099.3	PRSS12	-2.382047431	0.011504455	0.999935062
ENSG00000267272.5	LINC01140	-2.36381814	0.008845053	0.997704562
ENSG00000112038.17	OPRM1	-2.359022699	0.039416197	0.999935062
ENSG00000283930.1	AL117339.5	-2.358639718	0.001623162	0.417608527
ENSG00000281344.1	HELLPAR	-2.288718105	0.000874057	0.302537262
ENSG00000101292.7	PROKR2	-2.270600477	0.015506483	0.999935062
ENSG00000259583.2	AC015712.2	-2.228088199	0.001022324	0.334416805
ENSG00000153993.13	SEMA3D	-2.223873074	0.002292795	0.518758747
ENSG00000162645.12	GBP2	-2.215924081	0.027000021	0.999935062
ENSG00000280422.1	AC115284.2	-2.213725154	0.015349229	0.999935062
ENSG00000024422.11	EHD2	-2.18257749	0.004951709	0.787390505
ENSG00000172380.5	GNG12	-2.158801659	0.025544435	0.999935062
ENSG00000131094.3	C1QL1	-2.158765454	0.038903716	0.999935062
ENSG00000233922.2	LINC01694	-2.134350885	0.001281615	0.371473689
ENSG00000234230.1	ZFX-AS1	-2.134108105	0.036947798	0.999935062
ENSG00000165168.7	CYBB	-2.122012053	0.007777845	0.967919048
ENSG00000260702.3	AL031713.1	-2.121095429	0.045985261	0.999935062
ENSG00000110090.12	CPT1A	-2.110774706	0.000810719	0.294664358
ENSG00000085741.12	WNT11	-2.098774504	0.045992098	0.999935062
ENSG00000147202.17	DIAPH2	-2.089347685	0.000337015	0.164771187
ENSG00000279587.1	AC006963.1	-2.079564128	0.034473721	0.999935062
ENSG00000070808.15	CAMK2A	-2.04915574	0.000259199	0.134889655
ENSG00000102290.22	PCDH11X	-2.047083315	0.014057802	0.999935062
ENSG00000077327.15	SPAG6	-2.007353193	0.039097922	0.999935062
ENSG00000112280.16	COL9A1	-1.970712522	0.008619615	0.990995906
ENSG00000261754.2	AC008555.1	-1.953632224	0.000362237	0.164771187
ENSG00000138696.10	BMPR1B	-1.943960855	0.02121112	0.999935062
ENSG00000188869.12	TMC3	-1.943825332	2.27E-05	0.017302542
ENSG00000164241.13	C5orf63	-1.922385625	0.021705238	0.999935062
ENSG00000125355.15	TMEM255A	-1.919153201	0.014970922	0.999935062
ENSG00000261829.1	AC009407.1	-1.898690415	0.016454295	0.999935062
ENSG00000106006.6	HOXA6	-1.893899861	4.24E-05	0.031282905
ENSG00000128298.16	BAIAP2L2	-1.877895848	0.00232721	0.518758747
ENSG00000145945.6	FAM50B	-1.877373347	0.009973111	0.999935062
ENSG00000188738.14	FSIP2	-1.87336287	0.01230738	0.999935062
ENSG00000184254.16	ALDH1A3	-1.843668604	0.00685749	0.936511246
ENSG00000089558.8	KCNH4	-1.832863786	0.046562937	0.999935062
ENSG00000174080.10	CTSF	-1.829197062	1.69E-07	0.00019402
ENSG00000118407.14	FILIP1	-1.799351104	0.00036699	0.164771187
ENSG00000261801.5	LOXL1-AS1	-1.786223652	0.029880098	0.999935062
ENSG00000129910.7	CDH15	-1.780409066	0.022601678	0.999935062
ENSG00000157856.11	DRC1	-1.771788977	0.018835187	0.999935062
ENSG00000165929.12	TC2N	-1.764108901	0.024679331	0.999935062
ENSG00000147041.11	SYTL5	-1.746329359	0.020266328	0.999935062
ENSG00000165553.4	NGB	-1.746322054	0.025267012	0.999935062

ENSG00000168356.11	SCN11A	-1.736650283	0.00049208	0.212597098
ENSG00000157502.13	MUM1L1	-1.729140436	0.01102458	0.999935062
ENSG00000126733.20	DACH2	-1.727468884	0.001961073	0.48284561
ENSG00000142173.14	COL6A2	-1.725512655	0.048487453	0.999935062
ENSG00000164251.4	F2RL1	-1.71833087	0.003745844	0.649790452
ENSG00000277149.4	TYW1B	-1.715496551	0.015259927	0.999935062
ENSG00000141934.9	PLPP2	-1.687766201	0.003213493	0.598232296
ENSG00000137507.11	LRRC32	-1.685312196	0.005997274	0.880292135
ENSG00000253931.1	AC105118.1	-1.682816767	0.006418151	0.924294416
ENSG00000229851.1	ARSD-AS1	-1.678302877	0.000704224	0.273310649
ENSG00000129534.13	MIS18BP1	-1.674830942	0.028500014	0.999935062
ENSG00000272462.2	U91328.1	-1.671837517	0.000574954	0.235094735
ENSG00000156535.14	CD109	-1.664908096	0.040091405	0.999935062
ENSG00000115363.13	EVA1A	-1.663236142	0.004296592	0.718126704
ENSG00000102007.10	PLP2	-1.662248569	0.031666914	0.999935062
ENSG00000065717.14	TLE2	-1.660063051	0.003806774	0.65539478
ENSG00000285744.1	AC083837.2	-1.658681038	0.000245282	0.130615668
ENSG00000115718.17	PROC	-1.657151725	0.029919942	0.999935062
ENSG00000173947.13	PIFO	-1.640880606	0.031182442	0.999935062
ENSG00000271361.1	HTATSF1P2	-1.639638903	0.043914559	0.999935062
ENSG00000155886.11	SLC24A2	-1.628391389	7.42E-06	0.006289051
ENSG00000176840.11	MIR7-3HG	-1.627558749	0.002859131	0.569290348
ENSG00000260918.1	AC107398.3	-1.606231385	0.018768587	0.999935062
ENSG00000268089.2	GABRQ	-1.592205032	0.00114329	0.363597845
ENSG00000259977.1	AL121578.3	-1.591525657	0.029477177	0.999935062
ENSG00000138772.12	ANXA3	-1.591385738	0.007636507	0.966081465
ENSG00000261150.2	EPPK1	-1.58898571	0.002099188	0.504019677
ENSG00000267470.5	ZNF571-AS1	-1.582367804	0.00088523	0.302537262
ENSG00000254166.2	CASC19	-1.578413507	0.048913029	0.999935062
ENSG00000140853.15	NLRC5	-1.569619674	0.034601116	0.999935062
ENSG00000186340.15	THBS2	-1.544546057	0.000741025	0.278163783
ENSG00000154134.14	ROBO3	-1.543685903	0.045018814	0.999935062
ENSG00000164932.12	CTHRC1	-1.543225118	0.017849362	0.999935062
ENSG00000162511.7	LAPTM5	-1.540687719	0.001409615	0.402363267
ENSG00000180287.16	PLD5	-1.533566151	0.043689085	0.999935062
ENSG00000176170.13	SPHK1	-1.520407692	0.017797397	0.999935062
ENSG00000243978.8	RTL9	-1.514527412	0.007115295	0.936511246
ENSG00000119681.11	LTBP2	-1.51344298	0.002928662	0.578107787
ENSG00000270504.1	AL391422.4	-1.509908334	0.005032003	0.794639965
ENSG00000105479.15	CCDC114	-1.504930186	0.048399065	0.999935062
ENSG00000166949.15	SMAD3	-1.496070245	0.001551891	0.417608527
ENSG00000196071.5	OR2L13	-1.495315069	0.031229326	0.999935062
ENSG00000259343.6	TMC3-AS1	-1.48231438	0.000155658	0.093796122
ENSG00000284269.1	MIR7855	-1.475368688	0.044663322	0.999935062
ENSG00000269001.2	AC092070.2	-1.466477328	0.023148829	0.999935062
ENSG00000155846.16	PPARGC1B	-1.458516836	0.008665208	0.990995906
ENSG00000136842.13	TMOD1	-1.449030583	9.06E-05	0.06098784

ENSG00000057704.12	TMCC3	-1.447226355	0.006519392	0.933006442
ENSG00000265972.5	TXNIP	-1.432452109	0.00142793	0.402363267
ENSG00000047597.6	XK	-1.423347898	0.00201592	0.491069601
ENSG00000140057.8	AK7	-1.412450993	0.013791269	0.999935062
ENSG00000157570.11	TSPAN18	-1.40548561	0.000217671	0.121326251
ENSG00000120907.17	ADRA1A	-1.402181047	0.000863989	0.302537262
ENSG00000188803.14	SHISA6	-1.398990794	0.000154612	0.093796122
ENSG00000006756.15	ARSD	-1.39232112	0.000363002	0.164771187
ENSG00000164694.16	FNDCC1	-1.38658349	0.049673049	0.999935062
ENSG00000102024.17	PLS3	-1.38574672	0.003079907	0.587697557
ENSG00000165118.14	C9orf64	-1.369585406	0.033721202	0.999935062
ENSG00000187653.11	TMSB4XP8	-1.366699845	0.018266492	0.999935062
ENSG00000165359.15	INTS6L	-1.366351433	0.001244968	0.370224321
ENSG00000259753.1	AC068234.1	-1.362267707	0.031005358	0.999935062
ENSG00000198400.11	NTRK1	-1.361747557	0.02981503	0.999935062
ENSG00000285756.1	BX890604.2	-1.35979527	0.001205218	0.369233823
ENSG00000285437.1	POLR2J3	-1.351465133	0.030367247	0.999935062
ENSG00000184838.14	PRR16	-1.350180773	0.005923588	0.880292135
ENSG00000181649.6	PHLDA2	-1.347352956	0.001225674	0.369282593
ENSG00000196739.14	COL27A1	-1.344160078	0.04050985	0.999935062
ENSG00000117115.12	PADI2	-1.342597444	0.008982078	0.999935062
ENSG00000174740.7	PABPC5	-1.341771319	0.000177626	0.101681723
ENSG00000181085.14	MAPK15	-1.341291496	0.030238629	0.999935062
ENSG00000137198.9	GMPPR	-1.336213434	0.020071159	0.999935062
ENSG00000178562.17	CD28	-1.326452767	0.031255822	0.999935062
ENSG00000135116.9	HRK	-1.315868165	0.001209387	0.369233823
ENSG00000164616.16	FBXL21	-1.313108614	0.035423312	0.999935062
ENSG00000232160.6	RAP2C-AS1	-1.309026365	0.000352534	0.164771187
ENSG00000112297.14	CRYBG1	-1.30711361	0.004541736	0.742833325
ENSG00000187135.7	VSTM2B	-1.306132494	0.001444252	0.402363267
ENSG00000270249.1	AC093668.1	-1.304800153	0.03817777	0.999935062
ENSG00000102271.13	KLHL4	-1.304212371	0.002333485	0.518758747
ENSG00000006210.6	CX3CL1	-1.301335392	0.042754785	0.999935062
ENSG00000173826.14	KCNH6	-1.292617466	0.046201264	0.999935062
ENSG00000027075.14	PRKCH	-1.282597415	0.044001498	0.999935062
ENSG00000072864.14	NDE1	-1.281423938	0.038423796	0.999935062
ENSG00000129675.15	ARHGEF6	-1.279753154	0.033708325	0.999935062
ENSG00000267645.5	AC105052.3	-1.268838659	0.011807714	0.999935062
ENSG00000179083.6	FAM133A	-1.268323734	0.009387904	0.999935062
ENSG00000165029.15	ABCA1	-1.267799059	0.003856356	0.658976472
ENSG00000178726.6	THBD	-1.267291163	0.021938254	0.999935062
ENSG00000104368.17	PLAT	-1.266989741	0.032143817	0.999935062
ENSG00000225614.2	ZNF469	-1.265209712	0.023172139	0.999935062
ENSG00000267368.1	UPK3BL1	-1.262409413	0.012546077	0.999935062
ENSG00000135519.7	KCNH3	-1.261086922	0.014164057	0.999935062
ENSG00000213937.3	CLDN9	-1.253100323	0.04701149	0.999935062
ENSG00000205542.10	TMSB4X	-1.24983564	0.000100101	0.065488665

ENSG00000169891.17	REPS2	-1.248871047	0.031279033	0.999935062
ENSG00000197747.8	S100A10	-1.24792301	0.003471812	0.611519649
ENSG00000134602.15	STK26	-1.242907455	0.014030818	0.999935062
ENSG00000130158.13	DOCK6	-1.237088946	0.008450046	0.990995906
ENSG00000204131.9	NHSL2	-1.236514977	0.010071549	0.999935062
ENSG00000091490.10	SEL1L3	-1.232458598	0.001576913	0.417608527
ENSG00000246731.2	MGC16275	-1.221887513	0.035824536	0.999935062
ENSG00000275221.1	HIST1H2AK	-1.220971073	0.037167296	0.999935062
ENSG00000143013.12	LMO4	-1.220722555	0.003407283	0.610038901
ENSG00000154783.11	FGD5	-1.211748245	0.013497492	0.999935062
ENSG00000164949.7	GEM	-1.202628737	0.037759078	0.999935062
ENSG00000165895.18	ARHGAP42	-1.19855094	0.015918	0.999935062
ENSG00000176928.5	GCNT4	-1.194315271	0.026358439	0.999935062
ENSG00000160588.9	MPZL3	-1.189550432	0.023604178	0.999935062
ENSG00000274956.2	NKAIN3-IT1	-1.188254487	0.003281113	0.601047341
ENSG00000235750.9	KIAA0040	-1.183695237	0.036852101	0.999935062
ENSG00000272512.1	AL645608.7	-1.183507382	0.017059498	0.999935062
ENSG00000147862.16	NFIB	-1.181565112	0.00737357	0.939540034
ENSG00000266248.1	AC011474.2	-1.17892849	0.033156212	0.999935062
ENSG00000249896.2	LINC02495	-1.177702953	0.002251159	0.515470425
ENSG00000184258.7	CDR1	-1.175183863	0.003462941	0.611519649
ENSG00000198759.11	EGFL6	-1.172952484	0.026119538	0.999935062
ENSG00000132386.10	SERPINF1	-1.16337291	0.007142392	0.936511246
ENSG00000113083.13	LOX	-1.148468386	0.038293957	0.999935062
ENSG00000257800.1	FNBP1P1	-1.145931011	0.030205394	0.999935062
ENSG00000233058.1	LINC00884	-1.142591782	0.042238689	0.999935062
ENSG00000067992.13	PDK3	-1.133863427	0.017819701	0.999935062
ENSG00000066248.14	NGEF	-1.132718306	0.025080409	0.999935062
ENSG00000100302.6	RASD2	-1.13134418	0.017662911	0.999935062
ENSG00000147255.18	IGSF1	-1.128554493	0.03002644	0.999935062
ENSG00000153721.18	CNKSRR3	-1.12737389	0.041191468	0.999935062
ENSG00000285628.1	AC126755.7	-1.119745047	0.042712758	0.999935062
ENSG00000101955.14	SRPX	-1.116338379	0.015232652	0.999935062
ENSG00000285541.1	AC005548.1	-1.113230456	0.008002472	0.983937209
ENSG00000135723.13	FHOD1	-1.110636084	0.013847382	0.999935062
ENSG00000100625.8	SIX4	-1.101630073	0.039984665	0.999935062
ENSG00000103888.16	CEMIP	-1.099393075	0.008562348	0.990995906
ENSG00000041982.15	TNC	-1.095082459	0.015129651	0.999935062
ENSG00000069482.6	GAL	-1.093445734	0.031135184	0.999935062
ENSG00000136267.13	DGKB	-1.09080471	0.012138472	0.999935062
ENSG00000082684.15	SEMA5B	-1.083284008	0.008035473	0.983937209
ENSG00000101846.6	STS	-1.075663633	0.000437467	0.192637077
ENSG00000101935.9	AMMECR1	-1.071079801	0.040266123	0.999935062
ENSG00000100276.9	RASL10A	-1.0660332	0.038855633	0.999935062
ENSG00000183908.5	LRRC55	-1.059898009	0.015125222	0.999935062
ENSG00000112378.11	PERP	-1.058721909	0.013055213	0.999935062
ENSG00000272114.1	AL136131.3	-1.058177103	0.02833373	0.999935062

ENSG00000145708.10	CRHBP	-1.05589845	0.008428088	0.990995906
ENSG00000227091.1	AL355990.1	-1.046159148	0.046338429	0.999935062
ENSG00000128805.14	ARHGAP22	-1.045937445	0.010321531	0.999935062
ENSG00000184381.18	PLA2G6	-1.034808526	0.017117017	0.999935062
ENSG00000140682.18	TGFB11	-1.022504188	0.02216975	0.999935062
ENSG00000215386.12	MIR99AHG	-1.014869575	0.022095044	0.999935062
ENSG00000278915.1	AC005609.3	-1.010640332	0.04598916	0.999935062
ENSG00000166435.15	XRRA1	-1.009321379	0.002496424	0.526535678
ENSG00000260121.1	AC138028.4	-1.008001298	0.041874738	0.999935062
ENSG00000145730.20	PAM	-1.004542783	0.006713492	0.935482803

Table 3. RNA seq differentially expressed genes

healthy UTX vs healthy miR-146a, SMA UTX vs SMA miR-146a, healthy UTX vs SMA UTX.
padj; adjusted p-value.