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Gene expression for HIV-associated dementia and HIV encephalitis in microdissected neurons 1: preliminary analysis

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Abstract: We analyzed gene expression in neurons from 16 cases divided into four groups, ie, human immunodeficiency virus (HIV)-associated dementia (HAD)/HIV encephalitis (HAD/HIVE), HAD alone, HIVE alone, and HIV positive alone. We produced the neurons using laser capture microdissection from cryopreserved basal ganglia (specifically globus pallidus). Gene expression in pooled neurons from each case was analyzed on GE CodeLink Microarray chips with 55,000 gene fragments per chip. One-way analysis of variance showed significant changes in expression of 197 genes among the four groups ($P < 0.005$). The three groups, ie, HAD/HIVE, HAD alone, and HIVE alone, were compared with the HIV-positive group using Fisher's least significant difference test, and associated gene expression changes were assigned to each of the three comparisons. Identified genes were associated with 159 functional categories and many of the genes had more than one function. The functional groups included adhesion, amyloid, apoptosis, channel complex, cell cycle, chaperone, chromatin, cytokine, cytoskeleton, metabolism, mitochondria, multinetwork detection protein, sensory perception, receptor, ribosome, noncoding miRNA, signaling, synapse, transcription factor, homeobox, transport, multidrug resistance, and ubiquitin cycle. Several genes were associated with other neurodegenerative and developmental diseases, including Alzheimer's disease, Huntington's disease, and diGeorge syndrome. Thus, a wide range of dysregulated biochemical processes was reported in neuroanatomically precise neurons. This line of investigation is useful and provides specific information about gene expression dysfunction in NeuroAIDS.

Keywords: NeuroAIDS, human immunodeficiency virus, dementia, encephalitis, laser capture microdissection, globus pallidus, neuron, genes, expression

Introduction

The term "NeuroAIDS" has been used generally to describe the involvement of the central nervous system in human immunodeficiency virus (HIV)-related disease. The neurodegenerative processes in HIV infection result in neurocognitive decline, which range in severity from asymptomatic neurocognitive impairment to minor neurocognitive disorder and to HIV-associated dementia (HAD). There have been changes in the definitions during the last decade that evolved to the current term used for these conditions, ie, HIV-associated neurocognitive disorders (HAND). The precise pathogenesis of neurodegeneration associated with HIV infection is still unclear. However, neurons are the final targets of the neurodegenerative process, and additional cells are involved as well. The concomitant damaged substrate exhibits brain inflammation that is associated with HIV infection, ie, HIV encephalitis (HIVE), and can also involve macrophage/microglial infiltration and astrocytosis.[1–5] Although

the incidence of HAND has decreased due to combination antiretroviral therapy and other treatments, in recent years the prevalence of HAND has actually increased. Several factors are responsible for this trend, including side effects of combination antiretroviral therapy, increased longevity of patients, and viral mutations including drug resistance.[5–10] The importance of psychiatric symptoms, including anxiety and depression, are relevant as well because they are components of the stressors to which the brain is subject.[2,6,10,11] Tissues from the cases utilized here derive from the period prior to the advent of HAND classifications and reflect earlier work.

Several studies of gene expression in culture and in postmortem brain tissue relate to gene expression in patients who died with HIVE and HAND and have been reviewed.[5,12–19] Most brain studies analyzed RNA purified from small aliquots of brain tissue dissected from postmortem specimens. One such study, for example, utilized the frontal cortex from five subjects infected with HIV-1 and four controls negative for HIV-1 using microarrays. These two groups were analyzed by K-means cluster analysis. Genes with perturbed expression were identified that included cell cycle, inducible nitric oxide, chemokine, splicing, synapse, ribosomal proteins, maltose binding protein, myelin proteolipid protein, N-methyl-D-aspartic acid receptor, myelin-associated glycoprotein, astrocytic protein, Notch 3, amyloid precursor protein, senescence, proteasome, ferritin, and signaling.[20] In related work, IFN-γ showed increased expression in brain tissue from patients who died with NeuroAIDS and drug abuse compared with controls, while other cytokines did not show elevation.[21] In another study, gene expression in gray matter from the frontal lobe was analyzed using microarrays comparing cases with HIVE versus control cases without HIVE. This study indicated that HIV-1 infection in brain tissue associated with HIVE resulted in neurodegeneration and interfered with genes that regulate the cytoskeleton, synaptic-dendritic integrity and function, and signaling, and induced a neuroinflammatory response. Seventy-four genes were downregulated and 59 genes were upregulated. Downregulated genes had functions related to signaling (phosphatidylinositol-3-kinase, Ras-Raf-MEK1), transcription, cytoskeleton (MAP-1B, MAP-2, tubulin, adducin-2), the cell cycle (p35, p39, CDC-L2, CDC42, PAK1), synaptic plasticity, and synaptic transmission (ion channels, synaptogyrin, synapsin II). Upregulated genes had functions related to signaling modulation (MEK3, EphB1), cytoskeleton (myosin, aduccin-3, radixin, and dystrobrevin), transcription (STAT1, OLIG2, Pax-6), neuroimmune response (immunoglobulin G, major histocompatibility complex, β_2-microglobulin) and antiviral response (interferon inducible).[22]

Gene expression profiles related to astrocytes were shown to have many similarities across differing brain tissues (from patients with HIV-1 dementia and from macaques infected with simian immunodeficiency virus) and included several human and murine astrocyte cell culture systems. The use of astrocyte culture systems in the study of NeuroAIDS is supported because of the similarity of gene expression profiles in brain tissue and cultured cells and because astrocytes constitute a large percentage of cells in brain tissue. Several in vitro studies utilized HIV-1 and HIV-1 proteins, ie, Tat, envelope glycoprotein gp120, or negative regulatory factor. The correspondence of gene expression perturbed in these systems and in the brain includes cytokines, chemokines, and their receptors, and is also consistent with astrocyte activation.[23,24]

Neuronal cell cultures are also model systems. For example, a neuronal culture model of the dysfunctional NeuroAIDS brain including drug abuse utilized eight treatment conditions ($2 \times 2 \times 2$), with and without each of cocaine, Tat, and envelope protein. Statistically significant perturbation of gene expression was demonstrated for 35 genes across all treatment conditions using one-way analysis of variance. Functions of these genes included signaling, immune-related functioning, and transcription control.[25]

Human brain cortex middle frontal gyrus gene expression profiles were compared for cases of HAD or milder cognitive dysfunction versus HIV-negative cases. This work focused on neuronal dysfunction and possible relationships with subcortical dementia. Genes studied were ionic conductance carriers that control membrane excitation. Overexpressed genes included calcium-driven K^+ channel, leak type of K^+ channel, adenosine receptor, serotonin receptor, and the gamma aminobutyric acid receptor subunit. Underexpressed genes included two voltage-gated K^+ channels, a Na^+ channel subunit, a neuronal type of voltage-sensitive Ca^{2+} channel, a metabotropic glutamate receptor, and the N-methyl-D-aspartic acid receptor subunit. Although unfractionated tissue was used, the perturbed gene expression was considered to stem from neurons because changed expression of these genes changes did not occur in gyral white matter and were not associated with overall changes in glial markers. Moreover, these changes occurred with HAD, with and without HIVE, and were not associated with increased inflammatory gene expression.[26,27] The Trojan horse model predicts that HIV-1-infected monocytes are a risk for brain penetration of

HIV-1 via monocyte trafficking into the brain.[28] Surface gene expression associated with such cells included CD14, CD68, CD14a, and HLA-DR.[29] Pulliam et al studied gene expression on CD14+ monocytes from HIV-infected cases. Cases with high virus load showed increased expression of sialoadhesin, CD16, CCR5, and MCP-1. However, proinflammatory cytokine gene expression (interleukin-1, interleukin-6, and tumor necrosis factor-α) was unchanged.[30]

Microarray analysis in a monkey model using frontal lobe tissue from simian immunodeficiency virus-infected brains identified 98 genes with altered expression. Genes expressed were associated with promoting macrophage entry into the brain and associated toxic products. Those significantly upregulated included proteins in infiltrating macrophages, endothelial cells, and resident glia (eg, CD163, Glut5, and ISG15). Proteins found in cortical neurons included cyclin D3, tissue transglutaminase, α1-antichymotrypsin, and STAT1.[31]

Laser capture microdissection has been used successfully in the study of several human brain diseases, including the HIV-1-infected brain, subacute sclerosing panencephalitis, Parkinson's disease, and Huntington's disease.[32–39] In the current study, only cases with HAD and HIVE (as well as HIV-1-positive controls) were used. Thus, work in NeuroAIDS has progressed to the point where cell-specific studies will be able to elucidate additional information using novel approaches. We report on gene expression in specific neuroanatomically defined neurons.

Materials and methods

Brain tissue

As previously described,[39] autopsied cryopreserved brain tissue was obtained from the National Institutes of Health-sponsored National NeuroAIDS Tissue Consortium sites[40,41] (Table 1). At each of the National NeuroAIDS Tissue Consortium sites, the diagnosis of HIV-1-positive individuals with and without HAD and HIVE was made based on premortem neurological and clinical neuropsychological examination of the patients and at postmortem by neuropathological examination. Each subject was given a diagnosis, using a standardized, algorithmic diagnostic worksheet to combine neurological, neuropsychological, functional, and laboratory information. Postmortem tissues were examined by board-certified neuropathologists to exclude subjects with opportunistic central nervous system infections, tumors, or other causes of dementia, such as Alzheimer's disease. Furthermore, most subjects were below the age at which a dementing neurodegenerative illness would be expected.[7,8,11–13,42] Tissue was dissected from the globus pallidus and embedded in optimal cutting temperature compound. Sections 10 microns thick were cut using a cryostat at –23°C. The cryosections were mounted on laser capture microdissection slides (Microoptics of Florida, Palm Beach, FL). Prior to laser capture microdissection, the slides were cryopreserved at –80°C in sealed Bakelite slide boxes containing drierite.[39]

Table 1 Patient demographics and diagnosis

Subject number	HAD	HIVE	Gender	Race	Ethnicity Hisp	Risk	Duration HIV infection Y	Age at death Y
1	+	+	M	Cauc	–	MSM	17	47.30
2	+	+	M	Cauc	+	MSM	4	44.13
3	+	+	M	Black	–	MSM	10	43.53
4	+	+	M	Cauc	–	MSM	3	35.42
5	+	–	F	Black	–	IDU	7	64.96
6	+	–	F	Cauc	–	BPR HS	3	58.27
7	+	–	M	Cauc	–	IDU	13	62.48
8	–	+	M	Cauc	+	HS IDU	12	33.10
9	–	+	M	Black	–	BPR HS MSM	12	46.75
10	–	–	M	Cauc	+	MSM	10	50.14
11	–	–	M	NaAI	–	MSM	15	42.41
12	–	–	M	Cauc	–	MSM	15	46.16
13	–	–	M	Cauc	+	MSM	8	34.65
14	–	–	M	Cauc	–	MSM	U	54.35
15	–	–	M	Cauc	–	U	23	39
16	–	–	M	Cauc	–	U	12	64.69

Notes: All patients HIV-positive; all tissues from globus pallidus; +, present; –, absent.
Abbreviations: HAD, HIV-associated dementia; HIVE, HIV encephalitis; Cauc, Caucasian; Hisp, Hispanic; NaAI, native Alaskan; Y, years; IDU, injection drug abuser; U, unknown; HS, heterosexual; MSM, men who have sex with men; BPR, blood product recipient (blood transfusion); Y, years.

Laser capture microdissection

Slides for laser capture microdissection were lightly stained with Nissl (Arcturus Inc, Mountain View, CA) and dehydrated using an ethanol series followed by xylenes as previously described.[39] A Leica laser microdissection microscope (Leica Corporation, Bannockburn, IL) was used for laser capture microdissection using standardized settings and the laser beam precisely followed the neuron's outer membrane. Only neurons with nucleoli were microdissected. No other cells had nucleoli.[39]

RNA purification

For each case and control tissue, batches of 200 microdissected single cell neurons were suspended in 20 μL of extraction buffer (Picopure RNA extraction kit, Arcturus Inc) and RNA was extracted. The batches were pooled from multiple cryosections of each tissue. A CapSure-ExtractureSure assembly incubation block with cover (Arcturus Inc) was used to house the tubes. The block was incubated for 30 minutes at 42°C to extract the RNA. The RNA was cryofrozen on dry ice and stored under liquid nitrogen.[39]

Gene expression analysis

Biotin-labeled cRNA was prepared by linear amplification of the poly (A)+ RNA population within the total RNA sample. Briefly, about 0.5 ng of total RNA (estimated by the number of cryosectioned cells used for RNA isolation) was amplified using a RiboAmp HS kit (Arcturus). After second-strand cDNA synthesis and purification of double-stranded cDNA, in vitro transcription was performed using T7 RNA polymerase in the presence of biotinylated uridine-5′-triphosphate. It must be noted as crucial in the method, that the quantity and quality of the cRNA were assayed by spectrophotometry followed by analysis on an Agilent Bioanalyzer (Agilent Technologies, Colorado Springs, CO). The quality of the cRNA is paramount to ensure nonbiased representation of labeled transcripts containing the complement of the probe sequences deposited on the array.[39]

Ten micrograms of purified cRNA were fragmented to uniform size and applied to CodeLink Human Whole Genome Bioarrays (GE Healthcare, manufacturer instructions) in hybridization buffer. The specifications, use, and descriptions of the GenUS BIOSYSTEMS CodeLink human CHIPS were as described previously.[43,44] CodeLink Human Whole Genome arrays comprise approximately 55,000 30-mer probes designed to probe conserved exons across the transcripts of targeted genes. These probes represent annotated, full length, and partial human gene sequences from major public databases. All fragmented samples were visualized on the Agilent Bioanalyzer to verify complete fragmentation to about 0.1 kb size before array analysis. Arrays were hybridized at 37°C for 18 hours in a shaking incubator, washed in 0.75 × tris sodium chloride EDTA (TNE) at 46°C for 1 hour, and stained for 30 minutes with Cy5-streptavidin dye conjugate. Arrays were then rinsed, dried, and scanned at 5 μm resolution with a GenePix™ 4000B scanner (Axon Instruments, according to manufacturer instructions and software).

Statistical analysis

Data production

CodeLink Expression Analysis software (GE Healthcare) was used to process the scanned images from arrays (gridding and feature intensity) and the data generated for each feature on the array were analyzed using GeneSpring software (Agilent Technologies). All control genes and genes that did not pass the quality control metrics of the manufacturer were removed from further analysis.[44]

To compare individual expression values across arrays, raw intensity data from each gene were normalized to the median intensity of the array. Only genes with values greater than background intensity in at least one treatment condition were used for further analysis. Using a ratio interpretation of the data and normalization of each gene to the median intensity across conditions, data were filtered by expression intensity for genes that did not vary by 50% across all samples within the experiment. These unchanging genes were also eliminated from further analysis. This set of present genes was filtered for genes that were within one standard deviation from the mean of replicates. The remaining qualified gene list was queried for genes in treated groups that had ratios >2.0 and <0.5 (two-fold changes) relative to controls. Gene identification based on the GE identifiers was further accomplished using standard websites.[43–46]

Statistical methods

The data from this two-way unbalanced cross-classification experiment were analyzed first using analysis of variance to find genes that were statistically significantly different among the four groups at $P \leq 0.005$. Following the analysis of variance, pairwise Student *t*-tests were performed using the mean square error from the analysis of variance to test the simple effects of (HAD^+ $HIVE^+$) versus HIV^+ control, (HAD^+ $HIVE^-$) versus HIV^+ control, and (HAD^- $HIVE^+$) versus HIV^+ control for each selected gene. These pairwise comparisons were used to find the simple effects giving

rise to the overall statistically significant difference among the four groups. Doing the pairwise comparisons this way is based on Fisher's least significant difference test, which is done only if the overall *F*-test is significant. Using this approach, the pairwise tests do not need to be adjusted for multiple comparisons because the experiment-wise error rate is controlled by the *F*-test.

Pathway analysis

Pathway figures and gene interactions were generated using Gene Network Central PRO.[47] Pathways were also analyzed using Ariadne Pathways Assist.[48]

Results

Gene expression changes

Sixteen globus pallidus specimens were used as a single experiment (Table 1). The means and standard errors of 197 genes are shown in Table 2. Of these genes, 150 were identified from the GE CodeLink, NCBI, and GeneCards websites. Table 2 also shows the *P* values for overall and simple effects. Three gene expression comparisons made were HAD with HIVE, HAD alone, and HIVE alone, each versus HIV^+ infected controls. Of the identified genes, HAD with HIVE versus HIV^+ showed 27 genes upregulated and 30 genes downregulated. HAD alone versus HIV^+ showed 108 genes upregulated and 22 downregulated. HIVE alone versus HIV^+ showed 65 genes upregulated and 33 genes downregulated. In all three comparisons, three genes showed simultaneous upregulation and three genes showed simultaneous downregulation. In addition, comparing HAD/HIVE, HAD alone, and HIVE alone versus HIV^+, the following gene expression shifts, respectively, were one up-up-down, up-down-up, down-up-up, up-down-down, two down-down-up, and three down-up-down (Table 2). The triply regulated genes were as follows: up-up-up, B3GALT1 (galactose transferase), FLJ14167 (potassium inwardly-rectifying channel), and an unidentified gene; up-up-down, NYD-SP26 (development), up-down-up, SLC44A5 (choline transporter-like protein 5), down-up-up, one gene unidentified; down-down-down, HoxD11/HoxD10 (transcription factor, homeobox-regulated development), TBC1D22A (GTPase activator); down-down-up, one gene unidentified, HNRPA1P5 (heterogeneous nuclear ribonucleoprotein A1 pseudogene 5); down-up-down, one gene unidentified, DNAJC3 (chaperone, interferon-induced, double-stranded RNA-activated protein kinase inhibitor), SLAMF6 (SLAM family member 6, CD2 surface receptor, membrane component); and up-down-down, SLC36A4 (amino acid transporter).

Gene expression groups

The identified genes and their functions are shown in Table 3. There are large numbers of functions and gene groups because many genes are in more than one group. The categories of these functions include adhesion cell, adhesion matrix, adhesion membrane, amyloid beta synthesis, amyloid beta precursor processing, apoptosis, apoptosis caspase activator, binding metal ion, binding nucleotide, binding GTP, binding heparin, binding phosphatidyl inositol, binding DNA, binding RNA, binding double-stranded RNA, biosynthesis, biosynthesis amino acid, channel complex Ca, cell cycle, cell differentiation, cell division, cell division arrest, channel potassium inward rectifier, chaperone, chaperone cochaperone, chromatin regulation assembly, chromatin regulation repair, collagen, cytokine, cytokine growth factor, cytoskeleton, microtubule, development nervous system, developmental protein, Alzheimer's disease, diGeorge syndrome, Huntington's disease, DNA polymerase, DNA repair, endoplasmic reticulum, endocytosis, esterase thio-acyl-CoA, exocytosis, factor viability, glutamate polyglutamylase, glutamyl transferase, glycan N-glycan processing, glycosylation N-linked, glycosylation O-linked, Golgi stack apparatus, Golgi clathrin coat, Golgi vesicle, G protein cycle, GTPase, heat shock, hydrogenase-like protein iron only, interferon induced pathway, lamin prelamin recognition factor, lamin prelamin binding protein, lamina nuclear, lipid biosynthesis, lipid phosphatidyl serine biosynthesis, lipid phospholipid biosynthesis, matrix cell, matrix extracellular, metabolism, mitochondrial electron transport, mitochondrial function, mitochondrial membrane, mitochondrial metalloproteinase protein, mitochondrial ribosomal protein, mitochondrial ribosome, motility cell, movement intracellular, mRNA transport, multinetwork protein, multinetwork detection protein or RNA, nucleopore, nucleopore mRNA transport, oligosaccharide biosynthesis, oligosaccharide hydrolase, oncogene, oxireductase, oxidase, peptidase, peptide cross-linking, perception sensory olfactory, perception sensory visual, proliferation cell, protease, protease endoprotease, protein biosynthesis, protein kinase, protein phosphatase, proteinase metallo, pseudogene, receptor AMPA, receptor cytokine, receptor cytokine ligand, receptor interacting protein, receptor NMDA, receptor glutamate, receptor glycophorin, receptor metabotropic, receptor nuclear interacting, receptor MHC class I, receptor MHC class I antigen presentation, ribosome, ribosome subunits, ribosome assembly, ribosome protein, ribosome protein synthesis, ribosome translation factor, ribosome translation initiation factor, RNA heterogeneous nucleoprotein, RNA noncoding, RNA miRNA, signaling ras

Table 2 Significant gene expression by one-way analysis of variance ($P < 0.005$)

Identifier	Probe	HAD + HIVE		HAD		HIVE		Control		Between groups	HAD + HIVE/ control	HAD/ control	HIVE/ control
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	*P*	*P*	*P*	*P*
1244	GE472453	0.84	0.15	0.58	0.21	1.97	0.06	0.50	0.12	0.000700			Up × 4 0.000084
1420	GE474010	0.84	0.11	0.16	0.08	2.51	0.92	0.45	0.19	0.001871			Up × 5 0.000411
2021	GE479725	0.47	0.08	0.49	0.28	1.55	0.27	0.35	0.07	0.001153			Up × 4 0.000135
2172	GE481051	0.38	0.22	0.47	0.03	1.95	0.16	0.67	0.15	0.001634			Up × 3 0.000805
2573	GE484741	0.33	0.11	2.06	0.40	1.09	0.32	0.69	0.17	0.001987		Up × 3 0.000946	
2642	GE485413	1.96	0.59	4.86	0.43	1.68	0.38	3.62	0.26	0.001570	Down × 0.5 0.008019		Down 0.5 0.013596
2830	GE487382	1.13	0.40	4.42	0.45	0.69	0.19	1.38	0.37	0.000711		Up × 3.2 0.000256	
3159	GE490114	1.10	0.07	1.30	0.15	–0.15	0.30	0.73	0.13	0.000793		Up 1.8 0.016324	Down × 0.2 0.002706
3289	GE491184	0.22	0.07	0.70	0.03	1.74	0.08	0.88	0.17	0.001857	Down × 0.3 0.008868		Up × 2 0.007956
3577	GE493533	1.37	0.26	4.09	0.63	1.01	0.08	1.26	0.25	0.000344		Up × 3.2 0.000070	
4180	GE498722	6.75	0.46	11.19	0.89	6.60	0.74	7.35	0.45	0.001320		Up × 1.5 0.000544	
4272	GE499400	1.25	0.16	0.07	0.19	-0.11	0.05	0.86	0.15	0.000980		Down × 0.1 0.006076	Down × 0.1 0.004390
4285	GE499526	0.82	0.19	0.79	0.15	3.68	1.50	0.61	0.19	0.001679			Up × 6 0.000226
4361	GE500216	0.67	0.44	0.94	0.59	7.47	3.64	0.78	0.17	0.001535			Up × 9.6 0.000262
4711	GE503208	0.26	0.24	0.41	0.06	1.64	0.22	0.95	0.09	0.000930	Down × 0.3 0.003938	Down × 0.4 0.026397	Up × 1.7 0.017107
5179	GE507524	5.82	0.33	12.17	1.22	6.98	1.16	7.33	0.46	0.000326		Up × 1.7 0.000222	
5674	GE512134	1.09	0.25	0.51	0.20	2.33	0.01	0.52	0.12	0.000310	Up × 2 0.028641		Up × 4.5 0.000049
6001	GE515097	1.71	0.25	4.23	0.45	1.26	0.08	1.96	0.25	0.000385		Up × 2.2 0.000185	
6005	GE515151	1.65	0.35	4.45	0.95	0.59	0.14	1.79	0.22	0.001354		Up × 2.5 0.000785	

6006	GE515161	0.98	0.17	3.29	0.57	0.07	0.10	0.92	0.33	0.001728		Up × 3.6 0.000681	
6064	GE515618	0.86	0.04	0.33	0.18	0.93	0.24	1.46	0.15	0.001903	Down × 0.6 0.012379	Down × 0.2 0.000273	
6121	GE516084	1.01	0.26	0.82	0.23	2.59	0.13	0.27	0.09	0.000029	Up × 3.7 0.005634	Up × 3 0.043188	Up × 9.6 0.000003
6204	GE516830	1.52	0.49	4.18	0.52	1.49	0.33	1.63	0.15	0.000731		Up × 2.6 0.000171	
6530	GE519581	0.80	0.08	0.11	0.10	1.25	0.01	0.76	0.12	0.001515		Down × 0.1 0.002112	Up × 1.6 0.026406
6580	GE519998	1.72	0.37	3.63	0.31	0.43	0.04	1.66	0.19	0.000224		Up × 2.2 0.000235	Down × 0.3 0.016562
7181	GE525253	0.79	0.27	3.78	0.57	0.67	0.61	1.16	0.32	0.001331		Up × 3.3 0.000519	
7348	GE526744	1.17	0.11	1.41	0.24	0.44	0.08	0.49	0.11	0.001054	Up × 2.4 0.002376	Up × 3 0.000538	
7400	GE527127	2.26	0.48	4.77	0.35	1.59	0.47	2.65	0.25	0.001536		Up × 1.8 0.001290	
7585	GE528706	2.73	0.43	4.51	0.40	1.03	0.13	3.48	0.30	0.001906			Down × 0.3 0.001693
7999	GE53107	0.80	0.23	0.97	0.02	5.69	2.15	1.18	0.29	0.000800			Up × 4.8 0.000188
8018	GE53116	1.69	0.25	5.07	0.76	0.95	0.15	1.49	0.45	0.001297		Up × 3.4 0.000290	
8334	GE53271	1.19	0.16	2.30	0.11	1.34	0.08	1.31	0.13	0.001547		Up × 1.8 0.000432	
9079	GE536414	0.92	0.17	2.87	0.18	1.67	0.00	1.74	0.18	0.000344	Down × 0.5 0.006496	Up × 1.6 0.001424	
9181	GE53692	0.90	0.37	2.63	0.62	5.06	0.56	1.81	0.37	0.001577			Up × 2.8 0.000869
9536	GE538621	1.56	0.05	1.08	0.05	0.50	0.24	0.36	0.15	0.000240	Up × 4.3 0.000038	Up × 3 0.004543	
9814	GE54005	1.32	0.15	2.45	0.40	0.98	0.23	0.82	0.15	0.001327		Up × 3 0.000157	
10760	GE54509	−0.17	0.13	0.78	0.15	0.54	0.13	1.05	0.17	0.001764	Down × 0.2 0.000203		
11409	GE548504	0.12	0.15	1.00	0.21	2.08	0.06	0.82	0.17	0.000776	Down × 0.1 0.014773		Up × 2.5 0.001615
11522	GE549123	0.69	0.10	0.16	0.19	1.58	0.60	0.21	0.05	0.000703	Up × 3.3 0.028739		Up × 8 0.000138
11545	GE549241	0.82	0.24	0.10	0.07	1.78	0.14	0.92	0.10	0.000684		Down × 0.1 0.002516	Up × 2 0.004963

(*Continued*)

Table 2 (*Continued*)

Identifier	Probe	HAD + HIVE		HAD		HIVE		Control		Between groups	HAD + HIVE/ control	HAD/control	HIVE/ control
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	*P*	*P*	*P*	*P*
11877	GE55094	1.46	0.34	3.82	0.49	1.27	0.26	1.08	0.25	0.000668		Up × 3.5 0.000087	
12206	GE55267	1.17	0.47	2.82	0.59	1.72	0.11	3.54	0.21	0.001579	Down × 0.3 0.000267		Down × 0.4 0.009922
12366	GE553476	2.88	0.99	9.99	1.81	1.84	1.15	3.96	0.61	0.001746		Up × 2.5 0.001028	
12612	GE554808	0.73	0.24	4.16	0.96	0.64	0.16	1.00	0.30	0.001054		Up × 4.2 0.000309	
12915	GE556336	0.84	0.27	3.90	0.73	0.78	0.07	0.93	0.33	0.001167		Up × 4.2 0.000262	
13339	GE558357	0.14	0.19	0.89	0.09	0.26	0.07	0.92	0.08	0.001035	Down × 0.1 0.000340		Down × 0.3 0.006495
14400	GE563896	0.83	0.16	1.03	0.11	1.13	0.38	0.07	0.13	0.001971	Up × 12 0.004071	Up × 15 0.001706	Up × 16 0.002432
14504	GE564415	0.60	0.23	0.56	0.15	2.61	0.47	1.20	0.19	0.001793			Up × 2.2 0.003328
14612	GE56503	1.15	0.09	3.73	1.00	0.86	0.34	0.46	0.14	0.000471		Up × 8 0.000052	
14700	GE565524	0.06	0.17	1.29	0.14	1.31	0.38	0.30	0.13	0.000847		Up × 4.3 0.001557	Up × 4.4 0.003941
14740	GE565731	0.79	0.26	0.98	0.18	2.58	0.42	0.58	0.12	0.000453			Up × 4.4 0.000049
14756	GE56583	0.84	0.04	1.58	0.08	0.12	0.20	0.97	0.15	0.001455		Up × 1.6 0.011588	Down × 0.1 0.003885
14820	GE566190	0.52	0.12	2.26	0.36	−0.28	0.32	0.92	0.23	0.000966		Up × 2.5 0.002864	Down × 0.3 0.014591
15762	GE57137	1.14	0.34	3.70	0.39	1.49	0.27	1.71	0.27	0.001871		Up × 2.2 0.001043	
16114	GE57325	0.72	0.07	0.45	0.38	2.74	0.98	0.61	0.13	0.001970			Up × 4.5 0.000363
16469	GE57516	1.10	0.21	0.54	0.08	−1.38	0.29	0.59	0.14	0.000036	Up × 1.9 0.044226		Up × 2.3 0.000018
16547	GE57557	1.31	0.36	3.88	0.77	1.37	0.44	1.01	0.17	0.000909		Up × 3.8 0.000120	
16823	GE576963	0.85	0.23	1.19	0.11	−0.74	0.39	1.15	0.12	0.000238			Down × 0.6 0.000033
17180	GE57883	0.83	0.24	1.27	0.30	2.06	0.08	1.92	0.09	0.001476	Down × 0.4 0.000391	Down × 0.7 0.020768	

17447	GE58018	0.94	0.30	1.00	0.15	4.28	1.64	1.60	0.07	0.001327			Up × 2.7 0.000814
17879	GE582514	0.82	0.06	0.71	0.09	1.52	0.10	0.73	0.06	0.000148			Up × 2.1 0.000021
17884	GE58255	1.40	0.17	2.52	0.27	0.73	0.10	1.81	0.12	0.000540		Up × 1.4 0.010039	Down × 0.4 0.002016
17947	GE58287	0.87	0.15	0.87	0.06	2.10	0.25	0.79	0.14	0.001773			Up × 2.7 0.000241
17974	GE583033	1.74	0.39	4.91	1.00	1.79	0.03	1.65	0.22	0.001220		Up × 3 0.000208	
18252	GE58460	3.79	0.69	14.65	1.81	2.42	0.17	4.73	1.48	0.001689		Up × 3.1 0.000624	
18384	GE585314	9.70	4.79	21.25	3.36	4.38	2.41	1.02	0.34	0.001385	Up × 9.5 0.026542	Up 20.8 0.000173	
18390	GE58535	2.51	0.55	6.87	0.91	2.37	0.79	2.81	0.35	0.000747		Up × 2.4 0.000210	
18598	GE58654	0.53	0.14	1.50	0.11	0.78	0.07	0.88	0.10	0.001930	Down × 0.6 0.043481	Up × 1.7 0.003111	
18634	GE586724	6.33	0.88	10.61	0.70	3.35	1.32	5.86	0.48	0.000747		Up × 1.8 0.000491	
18765	GE587496	4.55	0.54	7.64	0.60	1.30	1.39	4.99	0.48	0.001309		Up × 1.53 0.010656	Down × 0.3 0.003449
19105	GE58946	0.30	0.09	1.39	0.08	1.30	0.64	0.43	0.10	0.001714		Up × 3.2 0.001541	Up × 3 0.007821
19877	GE593831	9.97	0.86	17.17	2.23	8.78	0.70	10.32	0.63	0.001914		Up × 1.7 0.000625	
20353	GE596515	0.66	0.14	0.98	0.33	3.76	1.57	0.83	0.13	0.001767			Up × 4.5 0.000333
20752	GE59877	1.11	0.10	0.94	0.20	0.60	0.16	0.14	0.11	0.000576	Up × 8 0.000127	Up × 6.7 0.001325	
20798	GE599024	1.46	0.12	2.46	0.17	1.20	0.20	0.79	0.21	0.001002	Up × 6.8 0.027292	Up × 3.1 0.000110	
22253	GE609375	0.88	0.12	2.18	0.52	0.19	0.04	0.63	0.09	0.000591		Up × 3.5 0.000168	
22901	GE613705	34.79	3.54	59.02	4.98	26.20	1.77	33.46	2.98	0.001113		Up × 1.8 0.000351	
22971	GE61413	0.50	0.20	−0.08	0.10	1.06	0.07	0.92	0.11	0.001731	Down × 0.5 0.047341	Down × 0.1 0.000398	
23200	GE61539	0.66	0.18	1.84	0.15	−0.01	0.01	0.51	0.20	0.001552		Up × 3.6 0.000614	
23526	GE617302	4.95	0.46	11.10	1.36	4.38	0.78	6.26	0.60	0.000934		Up × 1.8 0.000818	

(*Continued*)

Table 2 (*Continued*)

Identifier	Probe	HAD + HIVE		HAD		HIVE		Control		Between groups	HAD + HIVE/ control	HAD/control	HIVE/ control
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	*P*	*P*	*P*	*P*
24052	GE620526	1.17	0.14	4.25	1.23	1.19	0.31	1.08	0.13	0.001876		Up × 4 0.000327	
24282	GE62190	1.06	0.26	2.46	0.35	0.47	0.11	0.86	0.14	0.000841		Up × 2.9 0.000221	
24756	GE624691	2.22	0.31	3.35	0.72	0.13	0.43	2.68	0.23	0.001680			Down × 0.26 0.000538
24982	GE626074	1.28	0.18	0.50	0.15	1.91	0.29	0.74	0.09	0.000561	Up × 1.7 0.012227		Up × 2.6 0.000323
25091	GE62673	0.36	0.12	0.38	0.20	1.76	0.20	0.62	0.07	0.000109			Up × 2.8 0.000068
25103	GE62681	1.62	0.23	0.23	0.23	0.39	0.08	0.69	0.11	0.000997	Up × 2.3 0.001279		
25830	GE631063	1.56	0.26	4.38	0.39	1.51	0.68	2.01	0.30	0.001123		Up × 2.2 0.000536	
26034	GE63224	0.90	0.09	0.36	0.19	0.10	0.13	0.68	0.05	0.001590		Down × 0.5 0.034863	Down × 0.1 0.002654
26491	GE636205	1.65	0.81	7.62	1.57	2.67	1.97	0.60	0.15	0.000358		Up × 12.7 0.000040	
26776	GE644246	0.68	0.14	0.59	0.07	4.58	2.02	0.86	0.18	0.001082			Up × 5.3 0.000243
26936	GE648477	0.72	0.28	3.55	0.64	0.63	0.49	1.79	0.27	0.001761	Down × 0.4 0.044409	Up × 2 0.005878	
27283	GE655391	0.88	0.25	0.62	0.21	1.99	0.02	0.65	0.06	0.001297			Up × 3.1 0.000188
27415	GE657626	1.45	1.00	10.05	1.64	3.32	2.11	1.46	0.16	0.000092		Up × 6.9 0.000015	
27568	GE660354	2.84	2.15	16.96	5.10	3.04	3.68	0.83	0.26	0.001685		Up × 20.4 0.000217	
28284	GE674173	0.49	0.15	0.31	0.21	2.58	0.29	0.71	0.13	0.000054			Up × 3.6 0.000024
28369	GE675994	1.20	0.44	4.05	0.49	0.99	0.32	3.97	0.48	0.001972	Down × 0.3 0.001275		Down × 0.2 0.004302
28502	GE678706	0.66	0.26	3.32	0.59	0.27	0.30	0.92	0.15	0.000126		Up × 3.6 0.000058	
28508	GE678803	1.13	0.52	1.20	0.35	4.44	0.20	1.07	0.14	0.000161			Up × 4.1 0.000023
28991	GE687963	8.69	0.83	17.80	2.65	7.22	0.58	8.82	0.76	0.000816		Up × 2 0.000225	
29168	GE691505	0.82	0.09	0.45	0.18	1.59	0.04	0.45	0.12	0.001285			Up × 3.5 0.000211

29917	GE705764	0.41	0.15	0.85	0.41	4.34	2.10	0.62	0.14	0.002083			Up × 7 0.000386
30069	GE708617	0.73	0.15	0.58	0.14	2.12	0.07	0.49	0.14	0.000308			Up × 4.3 0.000035
30107	GE709371	1.49	0.28	0.42	0.20	1.67	0.39	0.41	0.12	0.001897	Up × 3.6 0.001461		Up × 4.1 0.002802
30167	GE710687	0.75	0.24	3.37	0.61	0.57	0.47	1.23	0.26	0.001563		Up × 2.7 0.000954	
31250	GE726916	0.75	0.27	0.46	0.22	–0.51	0.32	1.31	0.09	0.000457	Down × 0.6 0.036268	Down × 0.4 0.007327	Down × 0.4 0.000065
31353	GE728396	1.92	0.21	4.77	0.95	1.03	0.03	1.31	0.30	0.000741		Up × 3.6 0.000122	
31404	GE729136	0.91	0.06	2.52	0.27	1.38	0.14	1.10	0.21	0.001999		Up × 2.3 0.000533	
31632	GE732434	–0.14	0.26	1.28	0.07	1.01	0.26	0.90	0.11	0.000750	Down × 0.2 0.000510		
32204	GE740641	0.66	0.16	0.44	0.09	1.69	0.25	0.83	0.10	0.001980			Up × 2 0.001889
32318	GE742294	37.00	3.06	112.77	24.65	28.60	4.16	40.01	5.04	0.000741		Up × 2.8 0.000208	
32836	GE749435	0.82	0.19	1.53	0.13	0.42	0.11	0.61	0.08	0.001171		Up × 2.5 0.000262	
33031	GE752199	1.23	0.11	3.73	0.15	1.34	0.08	1.87	0.34	0.001822		Up × 2 0.001571	
33193	GE754378	0.48	0.10	0.82	0.22	1.78	0.01	0.64	0.12	0.001454			Up × 2.8 0.000362
33293	GE755614	1.15	0.28	2.68	0.38	0.56	0.40	1.00	0.11	0.000748		Up × 2.7 0.000210	
33722	GE762426	1.07	0.37	4.09	0.34	1.24	0.17	1.69	0.36	0.001841		Up × 2.4 0.001030	
33921	GE765425	0.57	0.23	0.97	0.37	2.62	0.25	0.85	0.11	0.000699			Up × 3.1 0.000190
34083	GE767593	1.27	0.15	2.83	0.43	0.43	0.14	1.02	0.23	0.001286		Up × 2.8 0.000425	
34195	GE769111	0.48	0.16	0.75	0.21	2.09	0.05	0.91	0.15	0.001954			Up × 2.3 0.001541
34221	GE769398	4.54	0.37	8.74	1.20	5.05	0.30	4.71	0.37	0.001547		Up × 1.9 0.000312	
34239	GE769588	1.06	0.17	0.21	0.12	–0.30	0.22	0.54	0.09	0.000504	Up × 2 0.010348		Down × 0.6 0.002269

(*Continued*)

Table 2 (*Continued*)

Identifier	Probe	HAD + HIVE		HAD		HIVE		Control		Between groups	HAD + HIVE/ control	HAD/control	HIVE/ control
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	*P*	*P*	*P*	*P*
34398	GE772048	0.34	0.38	1.86	0.42	2.34	0.35	0.61	0.11	0.001556		Up × 3 0.005964	Up × 3.8 0.001863
35620	GE78986	0.06	0.26	0.75	0.16	1.38	0.10	0.96	0.08	0.001613	Down × 0.1 0.000770		
35666	GE790167	0.98	0.13	0.44	0.09	2.45	0.64	0.76	0.10	0.000205			Up × 3.2 0.000054
35761	GE79076	0.51	0.40	3.53	0.21	1.38	0.16	1.68	0.26	0.000473	Down × 0.3 0.013393	Up × 2.1 0.001299	
36075	GE79260	0.72	0.12	0.41	0.15	2.04	0.57	0.80	0.11	0.001484			Up × 2.6 0.000754
36101	GE79273	1.17	0.15	0.28	0.28	0.81	0.11	0.39	0.05	0.002042	Up × 3 0.000610		
36278	GE79382	1.41	0.25	2.75	1.40	8.59	3.08	0.36	0.18	0.000408			Up × 23.9 0.000045
36337	GE79415	1.38	0.17	0.53	0.35	−0.25	0.33	0.26	0.11	0.001504	Up × 5.3 0.000716		
36363	GE794289	0.52	0.05	0.32	0.09	1.69	0.02	0.67	0.11	0.000122		Down × 0.5 0.042183	Up × 2.5 0.000090
36885	GE797280	0.47	0.25	2.39	0.29	1.27	0.11	0.76	0.14	0.000298		Up × 3.1 0.000105	
36949	GE79764	0.72	0.10	2.07	0.29	0.75	0.42	0.52	0.11	0.000296		Up × 4 0.000035	
36990	GE79788	7.69	0.28	6.21	0.51	16.04	3.72	8.32	0.76	0.001578			Up × 1.9 0.000688
37273	GE799491	1.14	0.19	0.93	0.08	0.98	0.39	0.28	0.07	0.002032	Up × 4 0.000510	Up × 3.3 0.007183	Up × 3.5 0.011246
38007	GE80398	3.38	0.82	7.92	1.28	2.12	1.96	1.81	0.36	0.001087		Up × 4.4 0.000136	
38049	GE804261	1.07	0.08	0.55	0.06	0.11	0.09	0.59	0.07	0.000143	Up × 1.8 0.000503		Down × 0.2 0.003676
38070	GE804386	1.77	0.26	5.95	1.20	2.43	0.15	2.16	0.25	0.000569		Up × 2.8 0.000142	
38729	GE808417	1.26	0.13	0.32	0.08	0.37	0.26	0.78	0.11	0.001945	Up × 1.6 0.013220	Down × 0.4 0.024128	
38739	GE80847	2.88	0.87	7.00	0.44	4.61	0.74	3.87	0.21	0.001721		Up × 1.8 0.001012	
38813	GE80890	0.76	0.09	0.47	0.07	3.06	1.16	0.78	0.09	0.000529			Up × 4 0.000130

38882	GE809301	0.82	0.21	1.45	0.18	0.35	0.12	1.52	0.10	0.001306	Down × 0.5 0.003543		Down × 0.2 0.000511
39376	GE812224	1.13	0.27	10.48	1.77	0.47	0.19	1.28	0.57	0.000016		Up × 8.2 0.000004	
39516	GE813126	0.67	0.12	–0.32	0.42	1.46	0.40	0.38	0.07	0.001864		Down × 0.8 0.019764	Up × 3.8 0.004217
39690	GE81418	1.16	0.21	0.17	0.07	–0.11	0.26	0.85	0.12	0.001704		Down × 0.2 0.012339	Down × 0.1 0.003760
39743	GE81449	0.84	0.15	0.48	0.20	2.03	0.11	0.77	0.08	0.000133			Up × 2.6 0.000045
40333	GE81822	0.78	0.19	0.54	0.08	2.56	0.52	0.91	0.14	0.000622			Up × 2.8 0.000234
40551	GE819522	0.71	0.26	0.03	0.14	2.24	0.42	0.73	0.11	0.000413		Down × 0.1 0.022083	Up × 3.1 0.000409
40642	GE820114	1.23	0.12	0.13	0.16	0.58	0.12	0.95	0.12	0.001288		Down × 0.2 0.001056	
40690	GE820397	0.26	0.14	0.86	0.12	1.86	0.33	0.91	0.11	0.000378	Down × 0.3 0.004116		Up × 2 0.001571
41169	GE82307	8.51	0.56	15.50	1.93	4.70	0.07	13.41	1.16	0.001551	Down × 0.6 0.011658		Down × 0.4 0.001387
41665	GE82602	0.19	0.08	0.41	0.12	0.52	0.17	0.94	0.08	0.000503	Down × 0.2 0.000081	Down × 0.4 0.002870	Down × 0.6 0.026178
41868	GE82723	1.83	0.66	15.01	5.12	1.58	0.40	1.39	0.53	0.001319		Up × 10.8 0.000232	
41968	GE82785	0.20	0.22	0.35	0.06	2.72	0.63	0.78	0.21	0.000683			Up × 3.5 0.000531
42072	GE82842	0.26	0.35	3.59	0.76	0.95	0.96	1.12	0.20	0.001575		Up × 3.2 0.001088	
42550	GE831160	0.75	0.11	2.35	0.33	0.77	0.30	1.08	0.13	0.000489		Up × 2.2 0.000326	
42718	GE832143	1.19	0.07	1.01	0.06	0.39	0.13	0.42	0.13	0.001362	Up × 2.8 0.000453	Up × 2.4 0.005987	
42726	GE83218	0.98	0.06	2.36	0.51	0.57	0.05	0.54	0.15	0.000749		Up × 4.4 0.000098	
42766	GE832421	1.09	0.37	6.45	0.42	0.50	0.05	1.55	0.32	0.000002		Up × 4.2 0.000001	
42791	GE83256	3.96	1.01	16.40	3.16	2.46	0.19	6.93	1.35	0.001969		Up × 2.4 0.002094	
43138	GE83463	1.77	0.23	3.83	0.34	1.91	0.03	1.99	0.25	0.001924		Up × 1.9 0.000561	
43379	GE83611	3.40	0.44	4.97	0.57	0.40	0.52	2.31	0.26	0.000231	Up × 1.5 0.049468	Up × 2.2 0.000416	Down × 0.2 0.011517

(*Continued*)

Table 2 (*Continued*)

Identifier	Probe	HAD + HIVE		HAD		HIVE		Control		Between groups	HAD + HIVE/ control	HAD/control	HIVE/ control
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	*P*	*P*	*P*	*P*
43489	GE83679	0.37	0.11	1.46	0.09	0.57	0.07	1.00	0.07	0.000029	Down × 0.4 0.000145	Up × 1.5 0.003600	Down × 0.6 0.013388
43664	GE837848	1.16	0.20	–0.13	0.25	1.34	0.06	0.69	0.13	0.001488		Down × 0.2 0.005883	Up × 1.9 0.039977
44056	GE84011	1.31	0.21	0.29	0.10	1.07	0.21	0.43	0.10	0.001195	Up × 3 0.000529		Up × 2.5 0.020259
44077	GE84023	2.02	0.48	7.74	0.83	2.62	0.42	4.22	0.36	0.000066	Down × 0.5 0.005099	Up × 1.8 0.000324	
44304	GE84156	1.37	0.23	3.52	0.25	1.20	0.18	1.79	0.28	0.001824		Up × 2 0.001229	
44579	GE843174	0.91	0.16	2.40	0.19	0.31	0.08	1.07	0.22	0.001392		Up × 2.2 0.001287	
44682	GE84381	1.30	0.38	3.28	0.58	0.12	0.30	1.35	0.21	0.001817		Up × 2.4 0.001712	Down × 0.1 0.047180
44855	GE84488	0.79	0.05	1.05	0.20	0.64	0.03	1.35	0.07	0.001428	Down × 0.6 0.000912		Down × 0.5 0.000908
45018	GE84584	1.03	0.26	2.72	0.20	0.50	0.40	1.88	0.18	0.000773	Down × 0.5 0.015272	Up × 1.4 0.027500	Down × 0.3 0.003757
45247	GE847267	1.35	0.12	0.19	0.01	1.27	0.02	0.72	0.10	0.000099	Up × 1.9 0.000790	Down × 0.3 0.005713	Up × 1.8 0.010591
45905	GE85117	1.56	0.22	3.84	0.53	0.44	0.19	1.37	0.29	0.000584		Up × 2.8 0.000237	
46183	GE852630	0.42	0.12	0.51	0.12	0.00	0.06	1.04	0.12	0.001524	Down × 0.4 0.003474	Down × 0.5 0.015075	0 0.000469
46298	GE853311	1.67	0.14	3.81	0.87	0.92	0.65	1.09	0.21	0.001881		Up × 3.5 0.000299	
47318	GE859187	1.47	0.51	1.02	0.15	10.30	2.42	0.71	0.20	0.000003			Up × 14.5 0.000000
47492	GE86023	0.52	0.09	0.47	0.14	1.47	0.10	0.46	0.10	0.001037			Up × 3.2 0.000151
47510	GE86033	0.54	0.13	3.29	0.26	0.24	0.13	1.85	0.37	0.001128	Down × 0.3 0.015394	Up × 1.8 0.015119	Down × 0.1 0.018845
47839	GE86226	2.35	0.46	4.43	0.10	1.40	0.49	2.75	0.16	0.000599		Up × 1.6 0.001416	Down × 0.5 0.014709
47990	GE863123	1.62	0.19	0.58	0.23	0.31	0.08	0.64	0.11	0.000872	Up × 2.5 0.000392		
48005	GE86324	0.85	0.32	3.46	0.86	0.48	0.02	0.84	0.20	0.001703		Up × 4.1 0.000413	

48087	GE863731	1.51	0.21	0.07	0.22	0.06	0.13	0.87	0.12	0.000481	Up × 1.7 0.012794	Down × 0.1 0.006535	Down × 0.1 0.014301
48127	GE86393	0.59	0.17	2.27	0.18	1.03	0.17	0.67	0.18	0.000430		Up × 3.4 0.000085	
48128	GE86394	2.43	0.35	8.01	1.16	3.88	0.30	3.35	0.64	0.002059		Up × 2.4 0.000712	
48161	GE86416	1.43	0.07	0.45	0.04	1.04	0.25	0.50	0.13	0.000774	Up × 2.9 0.000190		Up × 2.1 0.034611
48356	GE865354	28.90	1.02	27.32	5.38	89.57	23.60	28.03	2.13	0.000104			Up × 3.2 0.000017
48491	GE86614	0.78	0.10	0.61	0.21	1.52	0.03	0.45	0.09	0.001534			Up × 3.4 0.000178
49316	GE871079	0.52	0.13	1.09	0.20	1.32	0.26	0.27	0.08	0.000743		Up × 4 0.000907	Up × 4.9 0.000393
49481	GE87211	1.47	0.24	1.83	0.18	−0.19	0.06	1.08	0.19	0.002047		Up × 1.7 0.031097	Down × 0.2 0.003962
49512	GE87230	1.06	0.23	2.90	0.41	1.34	0.05	0.87	0.16	0.000390		Up × 3.3 0.000049	
49941	GE87458	0.74	0.31	3.16	0.81	0.29	0.04	0.89	0.17	0.001867		Up × 3.6 0.000681	
51072	GE880744	6.13	0.78	12.28	1.17	5.23	0.08	6.53	0.56	0.000468		Up × 1.9 0.000167	
51170	GE88133	0.77	0.18	8.17	0.18	0.91	0.66	1.11	0.21	0.000000		Up × 7.4 0.000000	
51284	GE88203	0.08	0.20	0.75	0.11	0.30	0.09	1.01	0.06	0.000342	Down × 0.1 0.000057		Down × 0.3 0.003714
51549	GE88364	5.64	0.04	15.48	3.73	5.01	0.14	5.35	0.58	0.001288		Up × 2.9 0.000244	
52061	GE88659	0.57	0.03	2.89	0.68	0.59	0.34	0.23	0.21	0.000509		Up × 12.6 0.000062	
52255	GE887730	2.62	0.37	5.14	0.65	1.16	0.25	2.40	0.37	0.002039		Up × 2.1 0.000990	
52268	GE88782	0.15	0.36	11.58	4.37	0.89	0.08	0.85	0.15	0.001374		Up × 13.6 0.000321	
52992	GE894844	0.99	0.05	0.27	0.04	0.45	0.13	1.09	0.12	0.001294		Down × 0.2 0.000376	Down × 0.4 0.006590
53339	GE898157	0.31	0.24	0.47	0.18	2.12	0.43	1.32	0.16	0.001107	Down × 0.2 0.003007	Down × 0.4 0.014878	Up × 1.6 0.040358
53778	GE902064	1.41	0.21	0.66	0.09	1.92	0.40	0.52	0.11	0.000618	Up × 2.7 0.001362		Up × 3 0.000268
54138	GE905236	1.11	0.26	3.16	0.15	1.25	0.13	1.20	0.28	0.001997		Up × 2.6 0.000432	

Abbreviations: HAD, HIV-associated dementia; HIVE, HIV encephalitis; SE, standard error.

Table 3 Select expressed genes and functions[44–46]

Identifier	Probe	Alias	Functions and comments
1244	GE472453	2NbHMSP	Immune activation-like gene in multiple sclerosis.
1420	GE474010	GRIN2A	Mg ion binding. Ion transport. Plasma membrane integral.
2021	GE479725	HECW2	E3 ubiquitin-protein ligase that mediates ubiquitination of TP73. Acts to stabilize TP73 and enhance activation of transcription by TP73.
2172	GE481051	–	–
2573	GE484741	ANKRD11	Member of a family of ankyrin repeat-containing cofactors that interacts with p160 nuclear receptor coactivators and inhibits ligand-dependent transcriptional activation.
2642	GE485413	SYPL2	Transporter activity. Synaptic vesicle integral to membrane. Synaptophysin-like 2.
2830	GE487382	–	–
3159	GE490114	–	–
3289	GE491184	–	–
3577	GE493533	–	–
4180	GE498722	–	–
4272	GE499400	GNAQ	Nucleotide GTP binding GTPase. Signal transducer. Protein ribosylation. Signal transduction G protein coupled receptor signaling pathway. Plasma membrane. Cytoplasm heterotrimeric G protein complex.
4285	GE499526	–	–
4361	GE500216	–	–
4711	GE503208	–	–
5179	GE507524	–	–
5674	GE512134	NR4A1	Nuclear transcription factor. Translocation from nucleus to mitochondria induces apoptosis.
6001	GE515097	–	–
6005	GE515151	PML	Nuclear transcription factor. Protein ubiquitination ligase complex. Zn ion binding. Promyelocytic leukemia.
6006	GE515161	MKLN1	Cell motility. Cell matrix adhesion. Signal transduction. Cytoplasmic.
6064	GE515618	TAF4B	Nuclear initiation transcription factor. TFIID complex.
6121	GE516084	–	–
6204	GE516830	–	–
6530	GE519581	TMTC2	Transmembrane and tetratricopeptide repeat containing 2. Multipass membrane protein.
6580	GE519998	–	–
7181	GE525253	FNDC5	Fibronectin type 3 domain-containing 5.
7348	GE526744	APOB	Receptor binding lipid transporter. Heparin binding. Signal transduction. ER microsome.
7400	GE527127	–	–
7585	GE528706	–	–
7999	GE53107	BACH1	Transcription regulation. Nuclear factor. BTB and CNC homology 1. Basic leucine transcription factor 1 variant 1.
8018	GE53116	TLK2	Nuclear. ATP binding. Serine/threonine kinase. Transferase. Chromatin regulation assembly/ disassembly. Response to DNA damage stimulus. Tousled-like kinase 2.
8334	GE53271	TRAK2/ALS2CR3	Receptor binding. Intracellular transporter. Neurotransmitter transport. Cytoplasm. Plasma membrane. Amyotrophic lateral sclerosis 2 juvenile. Chromosome candidate region3.
9079	GE536414	ZDHHC5	Metal ion binding. Membrane integral. Zn finger DHHC-type containing 5.
9181	GE53692	B4GALT7	Galactosyl transferase. Mn ion binding. Xylosyl-protein. Carbohydrate metabolism. Proteoglycan metabolism. Protein modification. Golgi stack. Membrane integral. Xylosyl protein beta 1,4-galactosyl transferase polypeptide 7. Galactosyl transferase 1.
9536	GE538621	HIST1H2BC	Nucleosome assembly. DNA binding. Chromosome organization and biogenesis. Histone cluster 1, H2bc.
9814	GE54005	CEACAM7	Plasma membrane integral. Carcinoembryonic antigen-related cell adhesion molecule 7.
10760	GE54509	SEC6L1	Exocytosis protein transport. SEC6-like 1.
11409	GE548504	LOC387856	Hypothetical protein. Similar to expressed sequence AI836003 (GenBank).
11522	GE549123	PRR15	Hypothetical protein. LOC222171. Proline-rich 15 (PRR15).
11545	GE549241	NPIP	Nuclear pore complex interacting protein.
11877	GE55094	NUDCD1	HR85 islet cDNA similar 2.
12206	GE55267	ADAM28	Metalloendopeptidase. Zn ion binding. Proteolysis. Spermatogenesis. Membrane integral. Disintegrin and metalloproteinase domain 28 variant 1.
12366	GE553476	IAPP	Islet amyloid polypeptide. Like related beta-amyloid associated with Alzheimer's disease, can induce apoptotic cell death.
12612	GE554808	LOC283488	Proline-rich protein.

(*Continued*)

Table 3 (*Continued*)

Identifier	Probe	Alias	Functions and comments
12915	GE556336	MYO9A	Myosin, actin-based motor molecule, ATPase activity. Unconventional myosins, intracellular movement. Regulates Rho activity in neurons. Regulation of neuronal morphology and function.
13339	GE558357	ADAM23	Metalloendopeptidase. Integrin binding. Proteolysis. Cell adhesion. Central nervous system development. Plasma membrane integral.
14400	GE563896	B3GALT1	UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 1. Member of the beta-1,3-galactosyltransferase gene family. Encodes type II membrane-bound glycoproteins with diverse enzymatic functions using different donor substrates (UDP-galactose and UDP-N-acetylglucosamine) and different acceptor sugars (N-acetylglucosamine, galactose, N-acetylgalactosamine). RP11–367C11.1 Stratagene fetal retina.
14504	GE564415	–	–
14612	GE56503	HIP2	Huntington interaction protein 2. Ubiquitin-protein ligase-like activating enzyme. Ubiquitin cycle.
14700	GE565524	DUSP15	Protein tyrosine-threonine-serine phosphatase. Hydrolase.
14740	GE565731	–	–
14756	GE56583	FBLIM1	Zn ion binding. Adhesion. Cell shape. Cytoskeleton. Filamin binding LIM protein 1.
14820	GE566190	–	–
15762	GE57137	KIF14	ATP binding. Microtubule motor and movement. Microtubule-associated complex. Kinasin 14 family member.
16114	GE57325	NELL1	Structure. Ca ion binding. Cell adhesion. Nervous system development.
16469	GE57516	TNNI1	Actin and tropomyosin binding. Regulation of strital muscle contraction. Muscle development. Troponin complex. Slow twitch skeletal troponin1.
16547	GE57557	CDK5	ATP binding. Cyclin-dependent protein kinase 5. Cell cycle. Cell proliferation. Cell division.
16823	GE576963	SESN1	Response to DNA damage stimulus. Cell cycle and proliferation arrest. Nucleus.
17180	GE57883	SELL	Sugar binding. Cell adhesion and motility. Plasma membrane integral. Selectin-L. Lymphocyte adhesion molecule 1.
17447	GE58018	TFAM/ATP88	Transcription factor. Regulation from RNAP-1 promoter. Nucleotide binding. Mg ion binding. Phospholipid translocating ATPase. DNA-dep-DNA replication. Mitochondrion membrane integral. Transcription factor A.
17879	GE582514	–	–
17884	GE58255	GCKR	Enzyme inhibitor. Glucokinase regulator.
17947	GE58287	MGAT2	Alpha-1,6-mannosyl-glycoprotein2-beta-N-acetyl glucosaminyl transferase. N-linked glycosylation. Oligosaccharide biosynthesis. Membrane integral. Golgi stack.
17974	GE583033	–	–
18252	GE58460	BSMAP	Transmembrane protein 59-like brain-specific membrane-anchored protein. Modulates the O-glycosylation and complex N-glycosylation steps occurring during the Golgi maturation of amyloid precursor protein. Inhibits amyloid precursor protein transport to the cell surface and further shedding. C19Orf4.
18384	GE585314	CENTG2	ArfGAP with GTPase domain, ankyrin repeat, and PH domain 1. GTPase-activating protein for ARF1 and, to a lesser extent, ARF5. ADP ribosylation factor. Directly and specifically regulates adapter protein 3-dependent trafficking of proteins in the endosomal-lysosomal system. GAP activity stimulated by phosphatidylinositol 3,4,5-trisphosphate (PIP3) and, to a lesser extent, by phosphatidylinositol 4,5-bisphosphate (PIP2). Phosphatidic acid potentiates PIP2 stimulation.
18390	GE58535	–	C16Orf5.
18598	GE58654	APH1A	Plasma membrane integral protein ectodomain proteolysis. NOTCH receptor processing. Endoplasmic reticulum, Golgi stack. Anterior pharynx defective 1 homolog A.
18634	GE586724	–	–
18765	GE587496	BLK	ATP binding. Protein tyrosine kinase. Protein kinase cascade.
19105	GE58946	CASP3	Cysteine-type peptidase, caspase, apoptosis induction.
19877	GE593831	MAN1A2	Mannosyl-oligosaccharide-1,2-alpha-mannosidase. Ca ion binding. Hydrolase. Acts on glycosyl bonds. Carbohydrate metabolism. N-glycan processing. Membrane integral Golgi stack.
20353	GE596515	PTPRK	Integral transmembrane receptor tyrosine phosphatase. Hydrolase.
20752	GE59877	PTPN6	Protein tyrosine phosphatase. Hydrolase. Apoptosis. G protein coupled receptor protein signaling pathway. Intracellular. Cytoskeleton. Membrane.
20798	GE599024	PDZRN3	Ubiquitin-protein ligase. Zn ion binding. Protein ubiquitination complex.
22253	GE609375	ZCSL3	Heat shock protein binding. Metal ion binding. Unfolded protein binding. Protein folding.
22901	GE613705	–	–
22971	GE61413	POLDIP2	Nucleus. Polymerase DNA directed delta-interacting protein 2.
23200	GE61539	SMCR7L	RP5–1104E15.5.

(*Continued*)

Table 3 (*Continued*)

Identifier	Probe	Alias	Functions and comments
23526	GE617302	RSAFD1	tRNA-yW synthesizing protein 1 homolog. Wybutosine is a hypermodified guanosine with a tricyclic base at the 3-prime position adjacent to the anticodon of phenylalanine tRNA that stabilizes codon-anticodon interactions during decoding on the ribosome. Wybutosine biosynthesis pathway.
24052	GE620526	FMO5	Mono-oxygenase. Demethyl-aniline mono-oxygenase (N-oxide forming). Electron transport. Endoplasmic reticulum, microsomal. Membrane integral.
24282	GE62190	GNG3/GNG7	Signal transduction. Regulation of G protein coupled receptor protein signaling pathway. Heterotrimeric G protein complex. Guanine nucleotide binding protein gamma-7.
24756	GE624691	–	–
24982	GE626074	ZA52P	Gastric protein uncharacterized.
25091	GE62673	AASS	Lysine ketoglutarate reductase. Oxidoreductase. Saccharopine dehydrogenase. Electron transport. Lysine catabolism. Protein tetramerization. Mitochondrial. Aminoadipate semialdehyde synthase.
25103	GE62681	ROM1	Cell adhesion. Sensory and visual perception. Plasma membrane integral.
25830	GE631063	–	–
26034	GE63224	ETFA	Electron carrier and transport. Mitochondrial matrix.
26491	GE636205	HDHD1A	Haloacid dehalogenase-like hydrolase domain containing 1.
26776	GE644246	SIPA1L1	Signal-induced proliferation-associated 1-like protein 1. Interacts with DLG4, PDLIM5, PDLIM7, PROSAPIP1, actin cytoskeleton, HPV E6. Cytoplasm, cytoskeleton. Cell junction, postsynaptic density at cell membrane, dendritic spines hippocampal neurons, synaptosome.
26936	GE648477	SOX5	SRY-related HMG box (SOX) transcription regulation factor family. DNA dependent from RNAP2 promoter. Nuclear.
27283	GE655391	CDC73	Cell division cycle 73, Paf1/RNA polymerase II complex component. Tumor suppressor in transcriptional and post-transcriptional control pathways. Component of PAF protein complex, which associates with the RNA polymerase II subunit POLR2A and a histone methyltransferase complex. Facilitates association of 3' mRNA processing factors with actively transcribed chromatin. Cell cycle progression through the regulation of cyclin D1/PRAD1 expression.
27415	GE657626	PTDSS1	Transferase. Phosphatidyl serine biosynthesis. Phospholipid biosynthesis. Membrane integral.
27568	GE660354	C14ORF119	C14ORF119
28284	GE674173	GPR161	Rhodopsin-like receptor. Signal transduction. G protein coupled receptor protein signaling pathway. Membrane integral.
28369	GE675994	MRPL51	Mitochondrial ribosomal protein L51. Encoded by nuclear genes. Mitochondrial ribosomes (mitoribosomes) consist of a small 28S subunit and a large 39S subunit. They have an estimated 75% protein to rRNA composition compared with prokaryotic ribosomes, where this ratio is reversed. No 5S rRNA.
28502	GE678706	TTLL5	Tubulin tyrosine ligase-like protein family. Interacts with two glucocorticoid receptor coactivators, transcriptional intermediary factor 2, and steroid receptor coactivator 1. Coregulator of glucocorticoid receptor-mediated gene induction and repression. Alpha tubulin polyglutamylase. Involved in the side chain initiation step of the polyglutamylation reaction not elongation step.
28508	GE678803	SPG7	Paraplegin. Spastic paraplegia 7 (pure and complicated autosomal recessive). Cell matrix adhesion regulator. This gene encodes a nuclear-encoded mitochondrial metalloprotease protein that is a member of the ATPases associated with a variety of cellular activities protein family. Members of this protein family share an ATPase domain and have roles in diverse cellular processes including membrane trafficking, intracellular motility, organelle biogenesis, protein folding, and proteolysis. Mitochondrion membrane, multipass membrane protein.
28991	GE687963	USP8	Cysteine-type endopeptidase. Ubiquitin thiol esterase. Ubiquitin-dependent protein catabolism. Ubiquitin cycle. Cell proliferation.
29168	GE691505	–	–
29917	GE705764	NALP1	Nod-like receptor family, pyrin domain containing 1. Death effector filament-forming CED-4-like apoptosis protein. ATP binding. Caspase recruitment domain protein 7. Caspase activator. Enzyme binding. Apoptosis induction and regulation. Defense response to pathogen. Intracellular.
30069	GE708617	–	–
30107	GE709371	HRB	DNA, RNA, metal ion binding. mRNA export, nuclear pore. Regulation of GTPase.
30167	GE710687	CCDC7	Coiled-coil domain-containing 7.

(*Continued*)

Table 3 (*Continued*)

Identifier	Probe	Alias	Functions and comments
31250	GE726916	TBC1D22A	GTPase activator.
31353	GE728396	–	–
31404	GE729136	GGA1	Protein transporter and complex assembly. Intracellular Golgi stack protein transport. Membrane. Clathrin coat of transGolgi network vesicle.
31632	GE732434	TARSL2	Threonyl-tRNA synthetase-like protein 2, ligase.
32204	GE740641	–	–
32318	GE742294	DMTF1	Cyclin D binding MYB-like transcription factor 1. Contains a cyclin D-binding domain, three central MYB-like repeats, and two flanking acidic transactivation domains at the N-terminus and C-terminus. Induced by oncogenic Ras signaling pathway and functions as a tumor suppressor by activating the transcription of ARF-p53 pathway to arrest cell growth or induce apoptosis. Activates transcription of aminopeptidase N and plays role in hematopoietic cell differentiation. Transcription regulated by binding D-cyclins. Transcriptional activator activates CDKN2A/ARF locus in response to Ras-Raf signaling, thereby promoting TP53/p53-dependent growth arrest. Binds to the consensus sequence 5′-CCCG[GT]ATGT-3′. Isoform 1 may cooperate with MYB to activate transcription of the ANPEP gene. Isoform 2 may antagonize transcriptional activation by isoform 1.
32836	GE749435	MSI2	Nucleotide and RNA binding.
33031	GE752199	–	–
33193	GE754378	ELP4	–
33293	GE755614	GRM3	Metabotropic glutamate, gamma aminobutyric acid B-like receptor. Signal transduction. G protein coupled receptor signaling pathway. Negative regulation of adenylcyclase. Plasma membrane integral.
33722	GE762426	–	–
33921	GE765425	GRIA3	Glutamate receptor, ionotrophic, AMPA 3. AMPA-selective glutamate receptor 3. Excitatory. AMPA is alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate. AMPA receptors mediate fast excitatory synaptic transmission in the central nervous system and play a key role in hippocampal synaptic long-term potentiation and depression.
34083	GE767593	CACNB2	Voltage-gated Ca channel complex. Ca ion binding and transport. Neuromuscular junction development. Membrane fraction.
34195	GE769111	GPRI33 or GP133	–
34221	GE769398	MSI2	Nucleotide and RNA binding.
34239	GE769588	PTF1A	–
34398	GE772048	WDFY1	Phosphatidyl inositol and Zn ion binding. Nuclear. Early endosome. Cytosol.
35620	GE78986	JUB	Component of cellular adhesive complexes. Contributes to cell fate determination and regulates cell proliferation and differentiation. Involved in the regulation of actin cytoskeleton dynamics and cell migration. Contributes to linking of epithelial cell junctions through adhesive receptors to actin cytoskeleton. Signal transduction from cell adhesion sites to the nucleus. Regulates kinase activity of AURKA/Aurora-A for mitotic commitment. Component of interleukin-1 signaling pathway modulating interleukin-1-induced nuclear factor kappa-B activation by influencing the assembly and activity of the PRKCZ/SQSTM1/TRAF6 multiprotein signaling complex. Transcription complex formation on DNA. Interacts with AURKA/Aurora-A during mitosis and both proteins are phosphorylated in a complex. Interacts with CTNNA1/alpha-catenin and with F-actin. Interacts with LATS2 during mitosis and regulates organization of the spindle apparatus through recruitment of gamma tubulin to the centrosome. Interacts with GRB2 and PIP5 K1 A. Forms a complex with SQSTM1, PRKCZ, and TRAF6. Interacts with SLC1 A2. Located in the cytoplasm, cytoskeleton, cell membrane, cell junction, nucleus, and centrosome. Shuttles between cytoplasm and the nucleus. Localizes on centrosomes during G2-M phase. Preferentially colocalizes with cadherin-adhesive complexes at sites of cell-cell contact. LIM region interacts with CTNNA1. The preLIM region binds directly actin filaments. LIM-2 and LIM-3 domains mediate the interaction with the N-terminal region of AURKA. The association between LATS2 and JUB required the second LIM domain of JUB. Belongs to the Zyxin/Ajuba family. Contains three LIM zinc-binding domains.
35666	GE790167	–	–
35761	GE79076	ULBP3	Major histocompatibility complex class I receptor complex. Antigen presentation. Natural killer activation. Membrane. UL16-binding protein 3.
36075	GE79260	RAP1A	Small GTPase-mediated signal transduction. GTP binding. Intracellular protein transport. Cell cycle. Negative regulation of cell cycle progression. Membrane. Ras oncogene family (RAP1A).

(*Continued*)

Table 3 (*Continued*)

Identifier	Probe	Alias	Functions and comments
36101	GE79273	USF1	DNA-dependent specific RNA polymerase 2 promoter transcription factor and regulator. Nuclear. Upstream transcription factor 1. Secretogloblin, family 1 A member 1 (uteroglobin).
36278	GE79382	RPL7A	Structural constituent of ribosome. Protein biosynthesis. Ribosome biogenesis and assembly.
36337	GE79415	PSP	Hypothetical protein MGC17299.
36363	GE794289	–	–
36885	GE797280	–	–
36949	GE79764	SFRS11/PLEKHA5	RNA binding. Phosphatidyl inositol binding. Nuclear mRNA splicing factor via spliceosome. Arginine/Serine-rich 11. Plekstrin homology domain containing family A member 5 mRNA.
36990	GE79788	SAMD13	–
37273	GE799491	FLJ14167	KCNJN1. Potassium inwardly rectifying channel, subfamily J, member 12. Inward rectifier potassium channel Kir2.2v. IRK-2. ATP-sensitive inward rectifier potassium channel 1. Potassium inwardly-rectifying channel, subfamily J, inhibitor 1. Kir2.2v. Establishing action potential waveform and excitability of neurons. Voltage dependence regulated by concentration of extracellular potassium. Inwardly rectifying potassium channel blocked by divalent cations. Inward rectifier potassium channels allow potassium to flow into the cell rather than out of it. As external potassium is raised, the voltage range of the channel opening shifts to more positive voltages. Inward rectification is due to blockage of outward current by internal magnesium. Can be blocked by extracellular barium and cesium. The inward rectifier potassium channel family (also known as 2-TM channels) include the strong inward rectifier channels (KIR2.x), the G protein-activated inward rectifier channels (KIR3.x) and the ATP-sensitive channels (KIR6.x, which combine with sulfonylurea receptors). Structurally, the pore-forming subunit of KIR channels is the alpha subunit. It contains a single pore domain between two membrane-spanning regions. Four alpha subunits combine to form a tetramer, with the pore domain of each subunit contributing to the structure of the central pore. Heteromeric channels can also be formed within subfamilies, eg, KIR3.2 with KIR3.3.
38007	GE80398	AKR1C1/AKR1C2	Aldo-keto reductase family 1, member C2. Electron transporter. Bile acid transporter. Oxidoreductase. 20-alpha-hydroxy-steroid dehydrogenase. Trans-1,2-dehdrobenzene-1,2-diol dehydrogenase. Xenobiotic and lipid metabolism. Transport. Digestion. Steroid metabolism. Dehydrodiol dehydrogenase 2. Bile acid binding protein. 3-alpha-hydroxysteroid dehydrogenase type 3 (AKR1C2) transcript variant 1 mRNA. Canalicular bile acid transport. Cytoplasm. AKR1C1 mRNA.
38049	GE804261	LOC285626	Hypothetical protein.
38070	GE804386	RP9	Metal ion binding. Sensory and visual perception. RNA splicing. Nuclear. Retinitis pigmentosa. Autosomal dominant.
38729	GE808417	TXNL6	Thioredoxin-like protein 6. Nucleoredoxin-like protein. Rod-derived cone viability factor.
38739	GE80847	TGM7	Gamma glutamyl transferase. Ca ion binding. Acyl transferase. Peptide cross-linking. Transglutaminase 7.
38813	GE80890	COL5A1	Extracellular matrix structural constituent. Heparin binding. Phosphate transport. Cell adhesion. Collagen type V alpha 1. Cytoplasm.
38882	GE809301	–	–
39376	GE812224	MGC39606	Hypothetical protein. Nonprotein coding RNA 86. Cytogenetic band Xq26.3.
39516	GE813126	–	–
39690	GE81418	SULT2B1	Alcohol steroid sulfotransferase. Lipid and steroid metabolism. Cytoplasm. Sulfotransferase family, cytosolic, 2B, member 1.
39743	GE81449	GDF15	Cytokine. Growth factor. Signal transduction. Transforming growth factor beta-receptor signaling pathway. Cell-cell signaling. Extracellular space. Growth differentiation factor 15.
40333	GE81822	PYCR2	Pyrroline-5-carboxylate reductase family member 2. Oxidoreductase. Electron transport. Proline biosysthesis.
40551	GE819522	–	–
40642	GE820114	KIAA1370	Hypothetical protein. LOC5620.
40690	GE820397	–	–
41169	GE82307	IQCC	IQ motif-containing C.
41665	GE82602	HOXD11/HOXD10	Transcription factor related to RNAP II. Development. Nuclear. Homeobox D11/10. Development.
41868	GE82723	DGCR8	Double-stranded RNA binding. DiGeorge syndrome, critical region gene 8.
41968	GE82785	C7ORF26	Chromosome 7 Orf 26.

(*Continued*)

Table 3 (*Continued*)

Identifier	Probe	Alias	Functions and comments
42072	GE82842	NOX5	NADPH oxidase, EF hand Ca binding domain 5.
42550	GE831160	–	–
42718	GE832143	MSI2	RNA binding.
42726	GE83218	APBA2BP	Amyloid beta (A4) precursor protein binding family A member 2 binding protein. Transcript variants 1 and 2. Ca ion binding. Oxidoreductase. Protein secretion. Antibiotic biosynthesis. Protein metabolism. Regulation of amyloid precursor protein biosynthesis. Golgi cysternae. Nuclear. Cytoplasm. Endoplasmic reticulum membrane.
42766	GE832421	ACOT6	Acyl-CoA thioesterase 6.
42791	GE83256	NRIP2	Nuclear receptor interacting protein 2.
43138	GE83463	ATP2B4	Hypothetical protein. MGC5457, mRNA.
43379	GE83611	NYD-SP26	Testis development protein.
43489	GE83679	SLAMF6	SLAM family member 6. CD2 surface receptor. Membrane integral.
43664	GE837848	KCMK12	Voltage-gated K ion channel transport. Membrane integral.
44056	GE84011	–	–
44077	GE84023	TGM2	Protein-glutamine. Gamma glutamyl transferase. Ca ion binding. GTP binding. Acyl transferase. G protein coupled receptor. Signaling pathway. Peptide cross-linking. Positive regulation of cell adhesion. Extracellular matrix. Cytosol. Membrane.
44304	GE84156	–	–
44579	GE843174	–	–
44682	GE84381	–	–
44855	GE84488	–	–
45018	GE84584	–	–
45247	GE847267	SLC44A5	Solute carrier family 44, member 5; choline transporter-like protein 5.
45905	GE85117	NARF	Nuclear prelamin A recognition factor. Similarity to iron-only hydrogenase-like protein 2. Prenyl-dependent prelamin A binding protein. Prenylation and farnesylation at carboxyl terminal end for membrane attachment and protein interactions. On cysteine residue of carboxyl-terminal CaaX motif. Component of a prelamin A endoprotease complex. Cysteine residue is removed from prelamin A when it is endoproteolytically processed into mature lamin A. Co-localizes with the nuclear lamina.
46183	GE852630	–	–
46298	GE853311	KIAA0922	Transmembrane protein 131-like isoform-1.
47318	GE859187	–	–
47492	GE86023	EIF4A2	DNA and RNA binding. Translation initiation factor. Protein biosynthesis. Regulation of translational initiation. Eukaryotic translation initiation factor 4F complex.
47510	GE86033	DNAJC3	DnaJ (Hsp40) homolog, subfamily C, member 3. Interferon-induced, double-stranded RNA-activated protein kinase) inhibitor. Tetratricopeptide repeat family of proteins. Highly conserved J domain found in DNAJ chaperone family members. Involved in the unfolded protein response during endoplasmic reticulum stress. Co-chaperone of HSPA8/HSC70, stimulates its ATPase activity. Inhibits both autophosphorylation of EIF2 AK2/PKR and the ability of EIF2 AK2 to catalyze phosphorylation of the EIF2 A. Inhibits EIF2 AK3/PERK activity.
47839	GE86226	RPS23	Structural constituent of ribosome. Protein biosynthesis. Small ribosomal subunit protein S23.
47990	GE863123	–	–
48005	GE86324	TMED1	Transmembrane emp-24 domain-containing 1.
48087	GE863731	SLC36A4	Solute carrier family 36 (proton/amino acid symporter), member 4.
48127	GE86393	ATP2A2	ATP, Mg, and Ca ion binding. Calcium transport ATPase. Hydrolase acts on acid anhydrides. Transmembrane transporter. Cation transport. Cell adhesion. Metabolism. Epidermis development. Membrane fraction. Microsome. Plasma membrane integral. Sarcoplasmic reticulum.
48128	GE86394	CSNK1E	Nucleotide binding. Protein serine/threonine kinase. Casein kinase 1. Protein Tyrosine kinase. DNA repair. Signal transduction. Casein kinase 1 epsilon.
48161	GE86416	FDFT1	Mg ion binding. Farnesyl diphosphate farnesyl transferase. Oxidoreductase. Cholesterol biosynthesis. Isoprenoid biosynthesis. Membrane integral.
48356	GE865354	MGC39606	Nonprotein coding RNA 86. Xq26.3 chromosome band location. NCRNA00086.
48491	GE86614	OR2T35/OR2T2	Olfactory receptor. Signal transduction. G protein coupled receptor. Sensory olfactory perception. Membrane integral. Olfactory receptor, family 2, subfamily T, members 35 and 2.
49316	GE871079	KIAA1026	Kazrin isoform A.
49481	GE87211	–	–

(*Continued*)

Table 3 (*Continued*)

Identifier	Probe	Alias	Functions and comments
49512	GE87230	LRFN5	Leucine-rich repeat and fibronectin type 3 domain-containing 5.
49941	GE87458	FKSG24	Hypothetical protein. MGC12972 (FKSG24).
51072	GE880744	KIAA1754	Inositol 1,4,5-triphosphate receptor interacting protein. ITPRIP. Danger.
51170	GE88133	SL336 A4	Solute carrier family 36 (proton/amino acid symporter), member 4.
51284	GE88203	SLC9 A9	Sodium:hydrogen antiporter. Solute: hydrogen. Sodium ion binding. Sodium ion transport. Regulation of pH. Membrane integral. Solute carrier family 9 (sodium/hydrogen exchanger) isoform 9.
51549	GE88364	MAPK11	ATP binding. Protein serine/threonine kinase. MAP kinase. MP kinase and transferase. Response to stress. Signal transduction. Protein kinase cascade. Antimicrobial humoral response. Mitogen-activated protein kinase 11.
52061	GE88659	ZNRF2	Zinc and ring finger 2.
52255	GE887730	–	–
52268	GE88782	C10ORF118	CTCL tumor antigen HD-CL-01/L14–2.
52992	GE894844	GYPA	Glycophorin A sialoglycoprotein of the human erythrocyte membrane. Receptor for influenza virus and hepatitis A virus. Affects function of SLC4A1.
53339	GE898157	HNRPA1P5	Heterogeneous nuclear ribonucleoprotein A1 pseudogene 5.
53778	GE902064	–	–
54138	GE905236	ABCB11	ATP-binding cassette, subfamily B (MDR/TAP), member 11. Membrane-associated protein. Member of the superfamily of ATP-binding cassette transporters that transport various molecules across extracellular and intracellular membranes. MDR/TAP subfamily involved in multidrug resistance.

pathway, signal transduction, signaling transforming growth factor-β, signaling immediate early, spliceosome, splicing factor, splicing factor RNA, synaptic function, trafficking endolysosomal system, trafficking protein, transcription factor, transcription factor upstream, transcription factor antagonist, transcription promoter, transcription regulation at RNAP-1 promoter, transcription regulation at RNAP-2, transcription, homeobox (development), binding nucleotide, transferase acyl, transferase farnesyl, transferase steroid sulfo, transport antiporter (sodium-hydrogen), transport cation, transport carrier solute, transport intracellular, transport lipid, transport membrane associated, transport metal ion, transport multidrug resistance, transport neurotransmitter, transport phosphate, transport phospholipid, transport mRNA, transport protein, transport symporter amino acid, tRNA ligase, tRNA nucleotide modification, tRNA synthase, tubulin, tumor antigen, ubiquitin protein catabolism, ubiquitin cycle, ubiquitin pathway, and zinc finger.

Pathways

Figure 1 illustrates typical pathways and connections among seven select genes. The seven genes are *APOB*, *NECAB3* (*APBA2BP*), *GRIA3*, *IAPP*, *HOXD10*, *UBE2K*, and *NELL1*. Gene functions are shown in Table 3. The seven genes and their interconnected related pathways are: *APOB*, *IAPP*, and *NECAB3* (*Apba2BP*), the beta-amyloid pathway; *HOXD10* and *UBE2K*, the ubiquitination pathway; *GRIA3*, other glutamate receptors; and *NELL1*, signaling and amyloid production. These seven genes are interconnected via genes (inserted by the GenePro program) in overlapping pathways that broadly include signaling, transcription, amyloid, and ubiquitination pathways. Similarly, interconnections and pathways may be produced for the other 143 genes in Table 3, that are too numerous and complex to show in one figure.

Discussion

Of the 197 genes that showed significant expression changes in HAD/HIVE, HAD alone, HIVE alone, versus HIV$^+$, 150 genes were identified. These genes were members of 159 groups and functions. It is beyond the scope of this article to analyze the genes in detail and the ramifications of the disease state within which gene expression varied significantly. The groups and functions, within which the genes fall, overlap many of the cellular processes in neurons. Although several of these cellular processes may not be considered neuron-specific, they are most likely expressed as part of the stress and attempt-at-recovery processes that the neurons exhibit in HAD/HIVE, HAD, and HIVE, compared with the control HIV$^+$.

Broadly, the categories (with some descriptors) include adhesion (intercellular interactions), amyloid (implicated in damage to cognition in Alzheimer's disease), apoptosis (neuronal dysfunction and cell death, also certainly associated with the end state of loss of cognition), binding (of various metal and biochemical ions, crucial in cellular processes), channel complexes (components of ion transport within cells and the plasma membrane), cell cycle (attempts

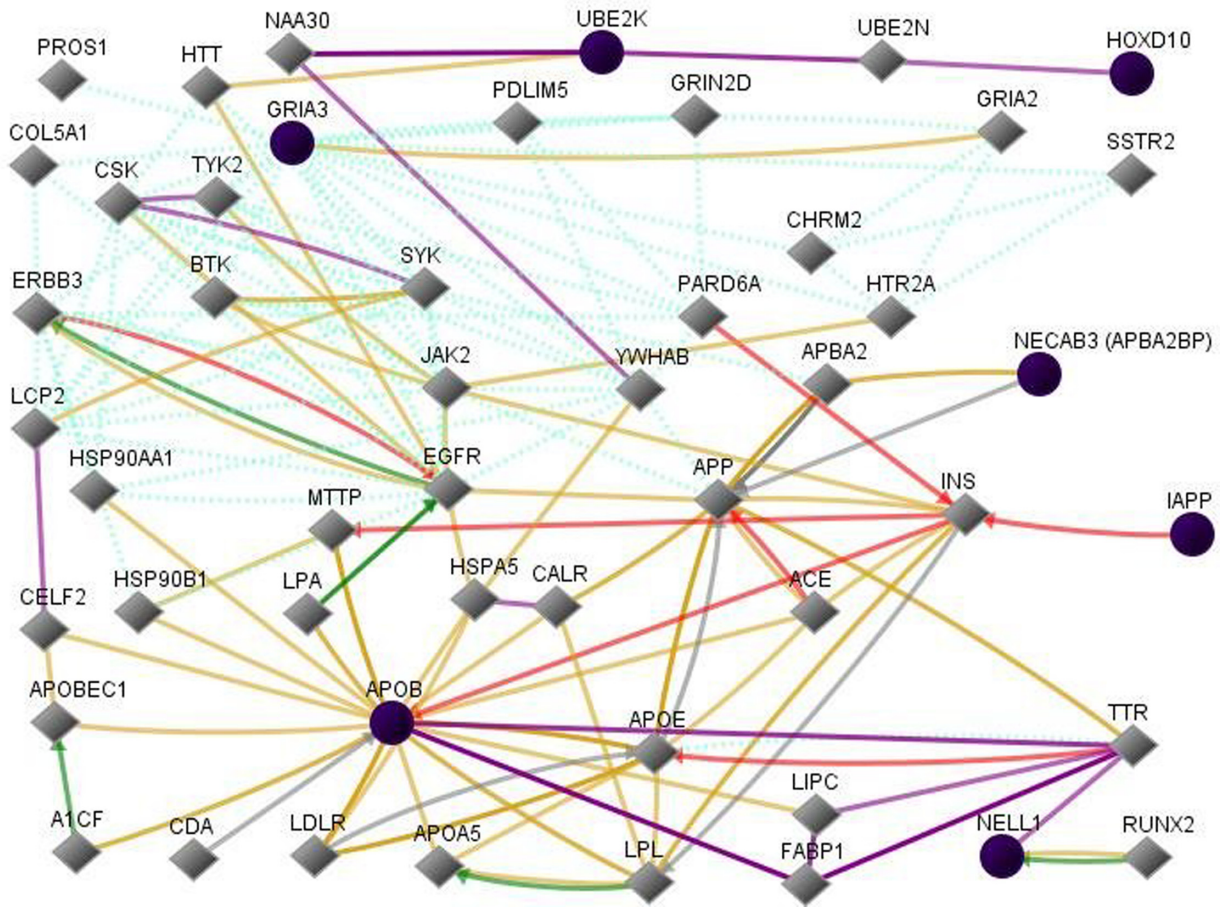

Figure 1 Pathway connections among *APOB*, *NECAB3* (*APBA2BP*), *GRIA3*, *IAPP*, *HOXD10*, *UBE2K*, and *NELL1*. The seven genes are indicated by solid circles. Diamonds indicate neighboring genes inserted by the GenePro program. Arrowheads indicate directional effects. The colors indicate the following: red, downregulation of function and transcription; green, upregulation of function and transcription; gray, regulation exists but direction unknown as yet; beige, gene products directly interact; dotted light blue, predicted protein–protein interaction; and purple, correlated expression detected by microarray experiments.[46] The seven genes are selected as representative of pathways including signaling, transcription, amyloid, and ubiquitination.

by the cell to expel noxious molecules through shutdown or traversing the cell division cycle), chaperone (assisting proteins to attain and maintain functional conformations), chromatin (central in transcription, genome maintenance and repair, and epigenetics), cytokines (inflammation), cytoskeleton, filaments, and matrix (scaffolding and intracellular transport), diGeorge syndrome (genes involved in brain development), and Huntington's disease (trinucleotide repeats that result in gene dysfunction), metabolism (breakdown of biochemical and cell components), mitochondria (energy production for the cell and also proteins needed for mitochondrion function and survival), multinetwork detection protein or RNA (proteins or RNAs that are involved in multiple different molecular pathways and networks), sensory perception (in this study, visual-related and olfactory-related protein expression was perturbed), receptor (binding that is required prior to an effect being exerted, signaling, by proteins and solutes), ribosome and tRNA (key elements in protein synthesis), noncoding miRNA (a novel realm in the control of gene expression), signaling (intracellular and extracellular molecular pathways), splicing (transcription), synapse (crucial in neuron function), transcription factor (proteins involved in initiation and process of transcription), transport (intracellular and intercellular movement of proteins and ionic and nonionic solutes), multidrug resistance (a process by which cells become resistant to drugs by shutting down their transport), and ubiquitin cycle (protein turnover). In addition, it should be noted that the ubiquitin pathway marks proteins for metabolism and degradation, whereas chaperones assist proteins to attain their optimal functional states.[26,49] We hypothesize the existence of multinetwork detection proteins and RNAs. Such proteins and RNAs would be involved in multiple unrelated molecular pathways and networks. This is consequently different from proteins that are involved in multiple, but related, pathways or homeobox transcription genes of development. For

example, MYO9A may be a multinetwork detection protein because it interacts with myosin filaments and actin-based motor molecules involved in intracellular movement, has ATPase activity, and regulates rho activity, integrin binding, proteolysis, cell adhesion, and central nervous system development.[45,46]

Potentially devastating effects for neuronal function and survival could result from gene expression changes in beta-amyloid-like protein and amyloid beta-A4 precursor protein binding family A member 2 binding protein. The effects of the former may be due to its amyloid-like properties and the effects of the latter, changes that may occur in amyloid precursor protein metabolism and signaling, due to changes in the receptor protein expression. In addition, changes in apolipoprotein B expression could be associated with dementia in NeuroAIDS as it is in Alzheimer's disease.[50] Severe changes in gene expression are anticipated, due to the stress that results from chronic HIV-1 infection of the brain. Accordingly, expression of glycophorin A is an example of such severe changes that can possibly occur in the neuron in NeuroAIDS. Glycophorin is a well known component of red blood cell membranes. The RNA that is purified in our procedures is free of all proteins and the detection method used is purely nucleic acid. Moreover, even if glycophorin mRNA were present in mature circulating red blood cells, red blood cells would not be present in our neuronal preparations, because we excise neurons from 10 micron thick sections (ie, smaller than the diameter of these neurons), the neurons are clearly identified with Nissl stain, and are the only cells with nucleoli in these sections. In addition, there were no endothelial cells associated with the neurons because of precision of excision by the laser beam. Likewise, red blood cells would be even further away from the excised neurons and well outside the laser excision perimeter. This greatly reduces the possibility of purifying and amplifying mRNA for glycophorin from red blood cells or any other potentially contaminating cells in our preparations. The glycophorin or glycophorin-like RNA that we detected, in all likelihood, is derived from anomalous glycophorin gene expression in the neurons we analyzed. Also, this is most likely due to the stress undergone by these neurons in their chronic state of disease.

This study is an initial step towards identifying specific genes in neuroanatomically specific neurons that may be involved in neurodegenerative processes that result from HIV-1 infection of the brain. Moreover, a wide range of biochemical processes in the health and maintenance of the cell are dysregulated. Some genes are novel, including for multinetwork detection proteins. This line of investigation is useful and will provide further specific information about dysfunction of gene expression in HAND.

Conclusion

Novel directions in the analysis and categorization of the transcriptome in disease and health are under development for HAND. For example, systems biological approaches are being developed to elucidate transcriptome organization patterns that are highly correlated across samples and that identify groups of genes or modules.[51] In addition, future prospective studies should be designed to answer additional questions, for example, related to virus load, symptomatology, as well as comparisons across the different stages in the evolution of diagnostic criteria for NeuroAIDS. It will also be of use to validate the data with additional patient cohorts.

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Disclosure

The authors report no conflicts of interest in this work.

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