The middle temporal gyrus is transcriptionally altered in patients with Alzheimer's Disease.

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We sought to understand, at the systems level and in an unbiased fashion, how gene expression was most different in the brains of patients with Alzheimer's Disease (AD) by mining published microarray datasets (1, 2). Comparing global gene expression profiles between patient and control revealed that a set of 84 genes were expressed at significantly different levels in the middle temporal gyrus (MTG) of patients with Alzheimer's Disease (1, 2). We used computational analyses to classify these genes into known pathways and existing gene sets, and to describe the major differences in the epigenetic marks at the genomic loci of these genes. While a portion of these genes is computationally cognizable as part of a set of genes up-regulated in the brains of patients with AD (3), many other genes in the gene set identified here have not previously been studied in association with AD. Transcriptional repression, both pre- and post-transcription appears to be affected; nearly 40% of these genes are transcriptional targets of MicroRNA-19A/B (miR-19A/B), the zinc finger protein 10 (ZNF10), or of the AP-1 repressor jun dimerization protein 2 (JDP2).

Keywords: Alzheimer's Disease, systems biology of Alzheimer's Disease, differential gene expression, middle temporal gyrus.

Alzheimer's Disease is a serious global health problem (4). Understanding how gene expression is altered in disease states can facilitate diagnosis, therapeutic target discovery, and an understanding of how the disease process manifests. By integrating findings from two independent studies (1, 2) that compared gene expression in the middle temporal gyrus (MTG) of patients with Alzheimer's Disease to that of the MTG in control subjects, we identified a set of 84 genes that, across both datasets, quantitatively changed in expression most significantly in patients with Alzheimer's Disease. 34 out of 84 genes are predicted to be transcriptional targets of the repressor jun dimerization protein 2 (JDP2), of the zinc finger protein 10 (ZNF10), or of the microRNA miR19A/B. An AACTTT motif not matching any known transcription factor motif can be found close to the transcription start site of 20 of the genes in this gene set. Elements of an endothelin signaling pathway gene signature emerged from Gene Ontology (GO) analyses. A subset of the genes in this set is involved in the synthesis and signaling of inositol triphosphate (IP3) and IP4. This gene set is significantly enriched for genes targeted by specific transcriptional repressors.

Methods

We used datasets GSE109887 (1) and GSE132903 (2) for these differential gene expression analyses performed using GEO2R. GSE109887 (1) was generated using Illumina HumanHT-12 V4.0 expression beadchip technology with n=32 for control subjects and n=46 for patients with Alzheimer's Disease. GSE132903 (2) was generated using Illumina HumanHT-12 V4.0 expression beadchip technology with n=98 for non-demented control subjects and n=97 for patients with Alzheimer's Disease.

1 The Benjamini and Hochberg method of p-value adjustment was used for ranking of
2 differential expression but raw p-values were used for assessment of statistical significance of
3 global differential expression. Log-transformation of data was auto-detected, and the NCBI
4 generated category of platform annotation was used.

5
6 A statistical test was performed to evaluate the significance of difference between mRNA
7 expression levels of each gene identified as differentially expressed in the middle temporal
8 gyrus of patients with Alzheimer's Disease as compared to the same region in non-affected
9 control subjects using a two-tailed, unpaired t-test with Welch's correction. Only p-values less
10 than 0.05 were considered statistically significant. Statistical analyses were performed using
11 PRISM 8.4.0(455).

12
13 For Gene Ontology (GO) analyses and Reactome pathway analysis, we used the
14 PANTHER online tool (5, 6). For analysis of enriched gene sets, we used the Broad Institute /
15 UC San Diego online tool Molecular Signatures Database (MSigDB) (7, 8). For computational
16 analysis of histone marks at the genomic loci of genes in this gene set, we used ENRICHr (9,
17 10).

20 **Results**

21 We mined data from two published microarray datasets to discover genes associated
22 with Alzheimer's Disease in the middle temporal gyrus, comparing global gene expression
23 profiles between patient and control (1, 2). We integrated data from both studies to discover
24 differentially expressed genes with high confidence.

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26
27 Comparing middle temporal gyrus transcriptomes in Alzheimer's Disease and in control subjects
28 identifies a set of 84 differentially expressed genes

1 We identified a set of 84 genes that was among the most differentially expressed genes
2 transcriptome-wide, across both datasets. Each of these genes was among the 250 most
3 differentially expressed genes measured by microarray when comparing global gene expression
4 in the middle temporal gyrus (MTG) of patients with Alzheimer's Disease (AD) to that of non-
5 demented control subjects (Figure 1; Table 1 and Table 2).

6
7 Next, we used a number of computational analyses to understand the molecular
8 signature of this gene set, including pathway analysis by over-representation and by searching
9 for overlap with existing gene sets, and we used a computational tool to determine whether any
10 specific histone modifications were enriched at the genomic loci of the 84 genes in this set.
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12 Molecular Signature Database (MSigDB) analysis demonstrates features of the gene set

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14 Gene set enrichment analysis (GSEA) utilizes global transcriptional data to identify gene
15 sets whose members are enriched in a dataset used as input based on determination of a
16 normalized enrichment score (NES) when comparing two conditions. As we integrated
17 microarray data from two separate studies of the AD MTG, we were interested to discover gene
18 sets sharing significant overlap only with the 84-member gene set identified here, rather than
19 discovering gene sets based on comparison of these datasets. Thus, we utilized the Molecular
20 Signature Database (MSigDB) online tool to identify gene sets that shared overlap with the gene
21 set identified here at a statistically significant level (Table 3). 26 genes out of 84 overlapped with
22 a set of genes previously identified to be up-regulated in the brains of patients with Alzheimer's
23 Disease by microarray ($p=9.84E-16$). Thus, by blindly selecting for genes that were among the
24 most differentially expressed in the AD MTG, and conserved across both datasets, we were
25 able to computationally label this gene set as sharing similarity at the molecular level with a set
26 of genes known to be up-regulated in brains of patients with Alzheimer's Disease. In addition to
27 describing the nature of this gene set by identifying similarity to other gene sets, MSigDB
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analysis identified a number of gene sets associated with specific molecular function. 20 out of 84 genes possessed at least one AACTTT motif ("M17") within 4 kb of the transcription start site; this motif does not resemble the binding site of any known transcription factor (p=4.23E-09). 3 out of 10 gene sets were associated with transcriptional repression by specific factors. This included 18 target genes of the jun dimerization protein 2 JDP2, as well as 12 target genes of the zinc finger protein 10 ZNF10 (p= 1.04E-07 and p=1.84E-07, respectively). For JDP2 and ZNF10 gene sets, target genes were defined by possession of a binding site in the promoter region. A third pathway associated with transcriptional repression was putative targets of the microRNAs miR19A and miR19B containing TTTGCAC in the 3' untranslated region (p=1.96E-07); 10 out of 84 genes in the set were predicted to be miR19A/B targets. Additional gene sets discovered included one associated with cadmium induction of DNA synthesis in macrophages (p=3.8E-08) , a set of genes down-regulated when comparing macrophages and B-cells (p=2.54E-07), and gene sets involved in positive regulation of developmental growth and developmental processes (p=2.06E-07 and p=7.23E-08, respectively).

Gene Ontology (GO) enrichment analysis reveals features of this 84-member gene set

GO enrichment analysis (PANTHER) revealed that this gene set shared similarity with a number of neurotransmitter, hormone and growth factor-like signaling pathways based on overlapping genes (Table 4). Pathways with overlapping genes included alpha adrenergic, oxytocin, histamine H1, and thyrotropin signaling pathways, with an overlap of 3 out of 25 genes for the alpha adrenergic system (p=1.97E-04), 3 out of 58 genes for the oxytocin pathway (p=1.96E-03), 3 out of 43 genes for the histamine H1 pathway (p=8.64E-04), as well as an overlap of 3 out of 60 genes for the thyrotropin-releasing hormone signaling pathway (p=2.15E-03). However, each of these overlaps was based on their usage of the same three

shared genes: PLCE1, PLCB1, and PRKCG, all components of IP3 signaling (discussed below). The enrichment of one signaling pathway, however, was specific and based on the occurrence of different components: the endothelin signaling pathway. 4 out of 82 genes in the endothelin signaling pathway ($p=4.17E-04$) were enriched for in this 84-member gene set; these included IP3 signaling genes PLCB1 and PRKCG but also included specific pathway components PCSK1 and RAF1.

In addition to specific signaling pathways, GO enrichment analysis highlighted that the process of transcriptional regulation was also affected, with 3 genes in this set overlapping with the 40 genes in total as part of the “General transcription regulation” pathway ($p=7.09E-04$), and 3 genes overlapping with the 59-member pathway involving transcriptional regulation by bZIP transcription factors ($p=2.06E-03$).

Of interest was a gene set enriched for enhancers bound by the PAX3-FOXO1 fusion in topologically associated domains (TAD). The PAX3-FOXO1 gene fusion is a hallmark of pediatric alveolar rhabdomyosarcomas and is caused by the $t(2;13)(q35;q14)$ chromosomal translocation (11). Nevertheless, 19 out of 84 genes in this gene set contained high-confidence PAX3-FOXO1 binding sites in restricted topologically associated domains of their enhancer regions ($p=5.23E-13$).

Inositol triphosphate synthesis and calcium signaling gene expression are perturbed in the MTG of patients with AD

Reactome pathway analysis revealed that synthesis of IP3 and IP4 in the cytosol was significantly enriched for in this gene set, with 4 genes overlapping with 26 genes in total as part of the IP3 and IP4 synthesis system (Table 5; $p=6.40E-06$). A previous study found that ITPKB

was differentially expressed in the frontal cortex of patients with Alzheimer's Disease (12). We found here that ITPKB was among the most differentially expressed genes in the MTG of patients with Alzheimer's Disease, expressed at significantly higher levels in AD (Figure 2 and Figure 3; $p < 0.0001$ for both datasets). NCALD, a neuronal calcium-binding sensor, was also among the genes most differentially expressed between the MTG of patients with AD and control subjects, and part of the 84-member gene set. NCALD was expressed at significantly lower levels in the MTG of patients with AD when compared to the MTG of control subjects (Figure 2 and Figure 3; $p < 0.0001$ for both datasets). Another IP3 signaling system component, the inositol 1,4,5-trisphosphate receptor interacting protein ITPRIP, also known as DANGER, was a part of the gene set identified here. ITPRIP was expressed at significantly higher levels in the MTG of patients with Alzheimer's Disease when compared to non-demented controls (Figure 2 and Figure 3; $p < 0.0001$ for both datasets).

A series of epigenetic marks that are enriched in the genomic regions of the gene set

We used ENRICHr to identify epigenetic marks shared among the 84 genes identified here (Table 6). The most significantly enriched modification was di-methylation of histone H3 at lysine 79, H3K79me2. In human embryonic stem cells (hESC), 17 out of 84 genes were marked by H3K79me2 ($p = 0.003572$), while 14 out of 84 genes were marked by H3K79me2 in human umbilical vein endothelial cells ($p = 0.038454$). Enriched marks included di- and tri-methylation of histone H3 at lysine 4 (H3K4me2 and H3K4me3), with H3K4me2 enrichment at 16 genes in mammary epithelial cells ($p = 0.008452$) and H3K4me3 at 15 genes in H1-hESCa, Caco-2 cells, and Jurkat cells ($p = 0.018675$, $p = 0.021007$ and $p = 0.024773$, respectively), as well as at 14 genes in NT2-D1 cells and astrocytes ($p = 0.038454$ and $p = 0.038454$). Tri-methylation of histone H3 at lysine 36 (H3K36me3) was enriched for, with H3K36me3 at 20 genes in megakaryocytes

($p = 0.023954$) and 16 genes in CD14⁺ monocytes ($p=0.008452$). Acetylation of histone H3 at lysine 9 and lysine 27 (H3K9Ac and H3K27Ac) was also enriched for, with H3K9Ac at 15 genes in H1-hESC ($p=0.018675$), 14 genes in HUVEC and lung fibroblasts ($p=0.038454$ for both), and 21 genes in K562 cells ($p=0.040878$), and with H3K27Ac at 16 genes in the spleen ($p=0.008452$), 15 genes in Panc1 cells ($p=0.018675$), and 14 genes in limb and in keratinocytes ($p=0.038454$ for both). We also found enrichment of tri-methylation of histone H3 at lysine 27 (H3K27me3), with H3K27me3 at 15 genes in testis (0.038454). The histone H2A variant H2AFZ was also significantly enriched for, with 15 genes possessing H2AFZ in skeletal muscle myoblasts and HepG2 cells ($p=0.018675$ for both), and 14 genes possessing H2AFZ in myotubes and B-cells ($p=0.038454$ for both).

In sum, we identified an 84-member gene set whose expression is dysregulated in the middle temporal gyrus of patients with Alzheimer's Disease and described its molecular features using computational analyses, identifying gene sets that shared similarity with this gene set, including the endothelin receptor signaling pathway and genes known to be disrupted in the brain of Alzheimer's Disease, as well as gaining insight into a potential role for transcriptional repression by JDP2, ZNF10 and miR19A/B. We also computationally ascertained which epigenetic marks are most enriched for at the genomic loci of the 84 genes of this set in various cell and tissue types; this included the histone modifications H3K79me2, H3K36me3, and H2AFZ.

Discussion

We compared global gene expression profiles in the middle temporal gyrus of patients with Alzheimer's disease to that of non-demented control subjects. We identified a gene set

1 containing 84 members whose expression was significantly dysregulated in patients with
2 Alzheimer's Disease. By computational pathway and enrichment analyses, we asked whether
3 we could determine molecular signature features of this gene set and gain insight into biological
4 function in Alzheimer's Disease by identifying gene sets that shared similarity to the one
5 identified here. We also assessed the epigenetic nature of the genes in this gene set, using
6 enrichment analysis of publicly available experimental data to determine which histone marks
7 were most commonly found at their genomic loci in a wide variety of tissues and cell types.
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10 GO enrichment analysis brought attention to the general process of transcriptional
11 regulation. Transcriptional regulation and histone modifications are closely related (13). MLLT6
12 is a negative regulator of histone H3 methylation at lysine 79 (H3K79me2). We found here that
13 MLLT6 was expressed at significantly higher levels in patients with Alzheimer's Disease in the
14 middle temporal gyrus. In human embryonic stem cells, H3K79me2 marks 17 out of 84 genes
15 in this gene set. In human umbilical vein endothelial cells, H3K79me2 marks 14 of 84 genes in
16 this set. H3K79me2 was the single most enriched for epigenetic mark in the gene set identified
17 here. Other epigenetic proteins in this gene set include CHD7, RBPJ and BRWD1; both CHD7
18 (14-17) and RBPJ (18-21) have established roles in brain development. Trans-acting factors
19 can also regulate transcription. Trans-acting factors (and factors similar to transcription factors)
20 in this gene set include NFKB, ZHX3, HOPX, and MZF1. NFKB immunoreactivity in the brain of
21 patients with Alzheimer's Disease in association with beta A4 diffuse plaques has been reported
22 (22); another NFKB pathway gene, NFKBIA, was also part of our gene set. Hopx has critical
23 roles in neural stem cells (NSC) of the periventricular zone (23) and potentially in NSC in the
24 hippocampus (24). Other proteins involved in transcription that were part of this gene set
25 include POLR2H, CTDSP2 and GTF2H3. CTDSP2 has an important role in NSC differentiation,
26 interacting and acting in concert with the repressor element 1 silencing transcriptional factor
27 REST/neuron-restrictive silencer factor (NSRF) complex; this involves a regulatory loop with
28

1 microRNA miR-26b (25). The AP-1 transcriptional repressor JDP2 was also part of our gene
2 set. Deletion of JDP2 has a protective effect on mice in a traumatic brain injury (TBI) mouse
3 model and TBI induces expression of JDP2 in the brain of mice (26).

4 We uncovered an endothelin signaling pathway gene signature in our gene set. One
5 study found that levels of beta-amyloid were significantly higher in endothelin-converting
6 enzyme knockout mice, demonstrating that endothelin-converting enzyme was important for
7 degradation of beta-amyloid *in vivo* (27). Other signaling pathways highlighted by our findings
8 include the nerve growth factor VGF and the platelet-derived growth factor receptor PDGFRB,
9 both part of our gene set. We also found significant enrichment of IP3 and calcium signaling
10 pathway components.
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12 The genes in this set may lend insight into mechanisms by which the disease process
13 occurs, or manifestations of the disease process itself. The relevance of these pathways to
14 Alzheimer's Disease must be studied in patient tissue. Analysis of enrichment histone marks in
15 the genes of this gene set in patients with AD must be verified by chromatin immunoprecipitation
16 of each of the marks in patient tissue. Multiple studies have previously published results of
17 microarray analyses from different regions of the brain in patients with Alzheimer's Disease, in
18 the amygdala, cingulate cortex, cerebral cortex, hippocampus, frontal cortex, and inferior
19 parietal lobe, each with differing differentially expressed genes (3, 12, 28-31). It is reasonable to
20 conclude that the way gene expression is altered in the brains of patients with Alzheimer's
21 Disease may be significantly different based on the portion of the brain being studied, and that
22 similar discrete sets of differentially expressed genes might be identified by integrating data
23 from multiple microarray datasets from the same tissue type.
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Figure 1: A set of differentially expressed genes in the middle temporal gyrus of patients with Alzheimer's Disease.

A heatmap of mRNA expression values from microarray data from Lardenoije et al. (left) and Piras et al. (right). Values are not scaled.

Gene Set Name	# Genes in Gene Set (K)	# Genes in Overlap (k)	k/K	p-value	FDR q-value
BLALOCK_ALZHEIMERS_DISEASE_UP	1669	26	0.0156	9.84E-16	2.53E-11
GRYDER_PAX3FOXO1_ENHANCERS_IN_TADS	1009	19	0.0188	5.23E-13	6.72E-09
AACTTT_UNKNOWN	1919	20	0.0104	4.23E-09	3.63E-05
BIOCARTA_CDMAC_PATHWAY	16	4	0.2500	3.8E-08	2.44E-04
GO_POSITIVE_REGULATION_OF_DEVELOPMENTAL_PROCESS	1428	16	0.0112	7.23E-08	3.72E-04
JDP2_TARGET_GENES	1880	18	0.0096	1.04E-07	4.46E-04
ZNF10_TARGET_GENES	803	12	0.0149	1.84E-07	5.26E-04
TTGCAC_MIR19A_MIR19B	515	10	0.0194	1.96E-07	5.26E-04
GO_POSITIVE_REGULATION_OF_DEVELOPMENTAL_GROWTH	189	7	0.0370	2.06E-07	5.26E-04
GSE3982_MAC_VS_BCELL_DN	195	7	0.0359	2.54E-07	5.26E-04

Table 3: Molecular Signatures Database (MSigDB) analysis describes the most significant features of this gene set based on overlap with existing gene sets.

Gene sets exhibiting significant overlap with the gene set identified here are listed in this chart, with p-value and false discovery rate (FDR) q-value.

Pathway	Total # genes in pathway	# genes shared with gene set	expected	fold enrichment	raw p-value	FDR
Alpha adrenergic receptor signaling pathway (P00002)	25	3	0.10	29.44	1.97E-04	3.22E-02
General transcription regulation (P00023)	40	3	0.16	18.40	7.09E-04	2.91E-02
Histamine H1 receptor mediated signaling pathway (P04385)	43	3	0.18	17.53	8.64E-04	2.83E-02
Oxytocin receptor mediated signaling pathway (P04391)	58	3	0.24	12.99	1.96E-03	5.36E-02
Transcription regulation by bZIP transcription factor (P00055)	59	3	0.24	12.77	2.06E-03	4.81E-02
Thyrotropin-releasing hormone receptor signaling pathway (P04394)	60	3	0.24	12.56	2.15E-03	4.41E-02
Endothelin signaling pathway (P00019)	82	4	0.33	12.25	4.17E-04	2.28E-02

Table 4: Gene Ontology (GO) enrichment analysis reveals an endothelin signaling pathway signature in this gene set.

Pathways from GO enrichment analysis exhibiting significant overlap with the gene set identified here are listed in this chart, with p-value and false discovery rate (FDR).

Reactome pathways	Total # genes in pathway	# genes out of 83 in this pathway	expected	fold enrichment	raw p-value	FDR
Synthesis of IP3 and IP4 in the cytosol (R-HSA-1855204)	26	4	0.11	37.74	6.40E-06	1.46E-02

Table 5: Reactome pathway analysis identifies enrichment of IP3 synthesis components.

Pathways from Reactome pathway analysis exhibiting significant overlap with the gene set identified here are listed in this chart, with p-value and false discovery rate (FDR).

Epigenetic Mark	Rank	Tissues / Cell Types	# of Genes	p-value(s)	Odds Ratio	Combined Score
H3K79me2	1; 20	hESC; HUVEC	17; 14	0.003572; 0.038454	2.023810; 1.686747	11.403559; 5.430502
H3K4me2	2	Mammary epithelial cell	16	0.008452	1.904762	9.092110
H3K36me3	3; 12	CD14+ monocyte; megakaryocyte	16; 20	0.008452; 0.023954	1.904762; 1.572624	9.092110; 5.868462
H3K27Ac	4 ; 7 ; 14; 23	Spleen; Panc1 human pancreatic cancer cell line; limb; keratinocyte	16; 15; 14; 14	0.008452; 0.018675; 0.038454; 0.038454	1.904762; 1.807229; 1.686747; 1.686747	9.092110; 7.108164; 5.430502; 5.430502
H2AFZ	5; 10; 16; 18	Skeletal muscle myoblast; HepG2 cell line; Myotube; B-cell	15; 15; 14; 14	0.018675; 0.018675; 0.038454; 0.038454	1.785714; 1.785714; 1.666667; 1.666667	7.108164; 7.108164; 5.430502; 5.430502
H4K20me1	6; 19	HUVEC; T-cell acute lymphoblastic leukemia	15; 14	0.018675; 0.038454	1.785714; 1.666667	7.108164; 5.430502
H3K4me3	8; 11; 13; 21; 24	H1-hESC; Caco-2 cell line; Jurkat cell line; NT2-D1 cell line; Astrocyte	15; 15; 15; 14; 14	0.018675; 0.021007; 0.024773; 0.038454; 0.038454	1.785714; 1.760192; 1.724495; 1.666667; 1.666667	7.108164; 7.062243; 6.377187; 5.430502; 5.430502
H3K9Ac	9; 17; 22; 26	H1-hESC; HUVEC; Lung fibroblast; K562 cell line	15; 14; 14; 21	0.018675; 0.038454; 0.038454; 0.040878	1.785714; 1.666667; 1.666667; 1.466706	7.108164; 5.430502; 5.430502; 4.689298
H3K27me3	15	Testis	14	0.038454	1.666667	5.430502
H3K4me1	25	Astrocyte	14	0.038454	1.666667	5.430502

Table 6: Epigenetic marks enriched in the genomic regions of the 84 genes found to be differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease based on ENCODE.

The most statistically significant enriched histone modifications at the genomic loci of each of the 84 genes was determined using ENRICHr analysis of ENCODE data. The rank of enrichment, tissue and cell type the data is derived from, number of genes in the gene set that marked by that histone modification in that tissue or cell type, p-value, odds ratio and combined score are listed for each of the gene sets most significantly enriched histone marks.

Figure 2: A set of genes differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease (1/4).

The exact mRNA expression levels of each of 84 genes in the gene set is displayed with mean mRNA levels for control non-demented middle temporal gyrus (MTG) (left) and AD MTG (right), along with p-value comparing the significance of difference in mRNA expression for that gene between control and diseased groups. This figure contains microarray data from the Lardenoij et al. study of the AD MTG.

Figure 2: A set of genes differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease (2/4).

Figure 2: A set of genes differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease (3/4).

Figure 2: A set of genes differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease (4/4).

Figure 3: A set of genes differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease (1/4).

The exact mRNA expression levels of each of 84 genes in the gene set is displayed with mean mRNA levels for control non-demented middle temporal gyrus (MTG) (left) and AD MTG (right), along with p-value comparing the significance of difference in mRNA expression for that gene between control and diseased groups. This figure contains microarray data from the Piras et al. study of the AD MTG.

Figure 3: A set of genes differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease (2/4).

Figure 3: A set of genes differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease (3/4).

Figure 3: A set of genes differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease (4/4).

Rank	ID	p-value	t	B	Gene
1	HSPB3	3.04E-12	-8.2638947	17.5188417	HSPB3
5	VGF	4.78E-11	-7.6437955	14.8863871	VGF
7	TMEM150A	8.35E-11	7.517665	14.3530528	TMEM150A
9	SERTAD3	1.36E-10	7.4078052	13.8894017	SERTAD3
10	STK38	1.61E-10	7.368258	13.7227224	STK38
12	CORO1C	2.42E-10	7.2762239	13.3353309	CORO1C
13	CTDSP2	2.44E-10	7.2741364	13.3265524	CTDSP2
15	RAF1	2.74E-10	7.2476543	13.2152268	RAF1
17	NFKB1	3.48E-10	7.1935687	12.9880657	NFKB1
18	NIPBL	3.79E-10	7.1740205	12.9060322	NIPBL
19	C15ORF57	4.43E-10	-7.1383481	12.7564324	C15ORF57
20	MLLT6	5.27E-10	7.0990803	12.5919063	MLLT6
21	ZNF438	5.52E-10	7.0882934	12.5467393	ZNF438
26	C17ORF102	6.84E-10	-7.0394367	12.3423261	C17ORF102
28	NFKBIA	7.27E-10	7.0253227	12.2833235	NFKBIA
30	STAG1	7.76E-10	7.0103257	12.2206544	STAG1
32	RHOQ	1E-09	6.9514919	11.9750553	RHOQ
34	ZNF184	1.2E-09	-6.911462	11.8081913	ZNF184
35	BRE	1.28E-09	-6.8951398	11.7402101	BRE
39	PDGFRB	1.91E-09	6.803298	11.3583355	PDGFRB
40	RBPJ	1.97E-09	6.7960626	11.328299	RBPJ
43	CHST6	2.02E-09	6.7905064	11.3052378	CHST6
44	HBP1	2.05E-09	6.7872784	11.2918423	HBP1
45	SLC7A2	2.07E-09	6.7854663	11.284323	SLC7A2
46	KIAA0556	2.07E-09	6.7852217	11.2833078	KIAA0556
48	NCALD	2.63E-09	-6.7303507	11.0558406	NCALD
50	GTF2H3	2.82E-09	-6.7140845	10.9884915	GTF2H3
54	PRKCG	3.12E-09	-6.6905105	10.8909541	PRKCG
58	HEY2	3.77E-09	6.647125	10.7116635	HEY2
67	CCKBR	4.37E-09	-6.6126595	10.5694397	CCKBR
78	NAP1L5	6.88E-09	-6.5072463	10.1356232	NAP1L5
79	PLCE1	7.22E-09	6.4961078	10.0898912	PLCE1
81	BRWD1	7.52E-09	-6.4866918	10.0512476	BRWD1
85	MCM7	8.82E-09	6.4494362	9.8984995	MCM7
87	NDUFAB1	8.88E-09	-6.4478014	9.8918026	NDUFAB1
88	BRF2	9.05E-09	-6.4434433	9.8739513	BRF2
89	SAP30L	9.13E-09	6.4413052	9.8651946	SAP30L
92	PLXNB1	1E-08	6.4193117	9.7751668	PLXNB1
95	ITSN1	1.05E-08	6.4086058	9.7313745	ITSN1
97	ATP6V1E1	1.08E-08	-6.4015781	9.7026393	ATP6V1E1
103	PLEKHH3	1.42E-08	6.338545	9.4453082	PLEKHH3
104	DDX39	1.43E-08	6.3363072	9.436186	DDX39

Table 1: A set of 84 genes differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease (1/2).

The rank of differential expression, the transcript ID, the p-value of differential expression, t, a moderated t-statistic, B, the log-odds of differential expression, and the gene name are listed in this chart, from GSE109887.

108	CHD7	1.56E-08	6.3162911	9.3546343	CHD7
109	FAM65C	1.56E-08	6.3155313	9.3515401	FAM65C
114	ARAP1	1.75E-08	6.2898438	9.2469974	ARAP1
116	TNIP1	1.86E-08	6.2742985	9.183793	TNIP1
119	CMTM4	2.04E-08	6.253428	9.0990119	CMTM4
120	B4GALT4	2.04E-08	6.2533925	9.0988679	B4GALT4
122	PCSK1	2.44E-08	-6.2107697	8.9259931	PCSK1
125	NINJ1	2.48E-08	6.2075505	8.9129513	NINJ1
128	INPP5D	2.52E-08	6.2031567	8.8951538	INPP5D
131	ITGA10	2.77E-08	6.180794	8.8046347	ITGA10
132	HOPX	2.79E-08	-6.1792137	8.7982419	HOPX
134	PRKAR1B	2.83E-08	-6.1762121	8.7861009	PRKAR1B
135	ITPRIP	2.83E-08	6.1759282	8.7849529	ITPRIP
139	EZR	3.19E-08	6.1478272	8.6713814	EZR
143	TRABD	3.31E-08	6.139462	8.6376054	TRABD
148	COPS8	3.48E-08	-6.1275561	8.5895583	COPS8
149	PLCB1	3.8E-08	-6.1064024	8.504266	PLCB1
156	TNS1	4.24E-08	6.080441	8.3997215	TNS1
157	KANK2	4.3E-08	6.0769751	8.3857755	KANK2
160	SCG3	4.52E-08	-6.0652366	8.3385628	SCG3
164	ITPKB	5.06E-08	6.038653	8.2317555	ITPKB
167	PEX11B	5.16E-08	-6.03377	8.2121538	PEX11B
179	C5ORF22	6.26E-08	-5.9878286	8.0279967	C5ORF22
180	C15ORF52	6.33E-08	5.9851511	8.0172788	C15ORF52
183	DHDDS	7.08E-08	-5.9585143	7.9107439	DHDDS
187	MZF1	7.27E-08	5.9521502	7.8853147	MZF1
190	TSPO	7.42E-08	5.9474896	7.8666987	TSPO
195	SLC5A3	7.65E-08	5.939979	7.8367093	SLC5A3
196	ENAH	7.66E-08	5.9397373	7.8357442	ENAH
210	CAPS	9.44E-08	5.8897294	7.6364111	CAPS
211	DPP6	9.55E-08	-5.8870729	7.625839	DPP6
215	FYCO1	9.75E-08	5.8820395	7.6058124	FYCO1
218	COL18A1	1.03E-07	5.869444	7.5557257	COL18A1
222	MRPS30	1.13E-07	-5.8468915	7.4661415	MRPS30
223	ILK	1.15E-07	5.8419792	7.4466452	ILK
225	TSPAN7	1.18E-07	-5.8364289	7.4246242	TSPAN7
227	POLR2H	1.21E-07	5.8303547	7.4005334	POLR2H
228	TUBB2A	1.21E-07	-5.8301615	7.3997673	TUBB2A
233	BTBD7	1.25E-07	5.8233002	7.3725662	BTBD7
235	NEDD8	1.27E-07	-5.8186542	7.3541544	NEDD8
237	NRN1	1.28E-07	-5.8161544	7.34425	NRN1
240	ZHX3	1.33E-07	5.8083153	7.3132016	ZHX3
242	PTRF	1.33E-07	5.8070545	7.3082092	PTRF

Table 1: A set of 84 genes differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease (2/2).

1	1	ILMN_1753426	4.74E-21	10.6130121	37.1655212	KIAA0556	KIAA0556
2	2	ILMN_2264625	1.42E-20	10.4509752	36.0944911	NIPBL	NIPBL, cohesin loading factor
3	3	ILMN_1678494	2.01E-20	10.3995164	35.7552697	ZNF438	zinc finger protein 438
4	4	ILMN_1708537	3.32E-20	10.3250844	35.2654153	RBPJ	recombination signal binding protein for immunoglobulin kappa J region
5	5	ILMN_2151048	4.64E-20	10.2751915	34.9376067	STAG1	stromal antigen 1
6	6	ILMN_1663195	7.6E-20	10.2017296	34.4557642	MCM7	minichromosome maintenance complex component 7
7	7	ILMN_2299612	7.62E-20	10.2013927	34.4535569	TMEM150A	transmembrane protein 150A
8	9	ILMN_2179018	1.68E-19	-10.0829023	33.6785041	NDUFAB1	NADH:ubiquinone oxidoreductase subunit AB1
9	10	ILMN_2160764	2.13E-19	10.0477788	33.4492786	HBP1	HMG-box transcription factor 1
10	12	ILMN_1714965	8.6E-19	9.83806	32.0857678	NFKB1	nuclear factor kappa B subunit 1
11	15	ILMN_1749838	1.99E-18	9.7113471	31.2664207	MZF1	myeloid zinc finger 1
12	16	ILMN_1773154	2.02E-18	9.708837	31.2502256	NFKBIA	NFKB inhibitor alpha
13	17	ILMN_1703650	2.21E-18	9.6957963	31.1661094	TNIP1	TNFAIP3 interacting protein 1
14	18	ILMN_1804652	2.49E-18	9.6773586	31.0472459	PLEKHH3	pleckstrin homology, MyTH4 and FERM domain containing H3
15	20	ILMN_1670881	6.2E-18	9.5389009	30.1571226	CHST6	carbohydrate sulfotransferase 6
16	21	ILMN_1742330	7.12E-18	9.5178513	30.0221888	PLXNB1	plexin B1
17	24	ILMN_1784447	1.6E-17	9.3941402	29.2313173	PLCE1	phospholipase C epsilon 1
18	26	ILMN_1786024	1.69E-17	9.3861149	29.1801412	POLR3H	RNA polymerase III subunit H
19	29	ILMN_1813489	1.85E-17	9.3719499	29.0898528	RAF1	Raf-1 proto-oncogene, serine/threonine kinase
20	30	ILMN_1815319	2.2E-17	9.3454004	28.9207603	CMTM4	CKLF like MARVEL transmembrane domain containing 4
21	33	ILMN_1772233	2.47E-17	9.3277893	28.8086934	ARAP1	ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 1
22	34	ILMN_2373779	2.54E-17	-9.3235712	28.7818635	COPS8	COP9 signalosome subunit 8
23	35	ILMN_1757781	2.61E-17	9.3193247	28.7548571	SAP30L	SAP30 like
24	36	ILMN_1720710	2.97E-17	-9.2991153	28.6263965	HSPB3	heat shock protein family B (small) member 3
25	37	ILMN_1801934	3.01E-17	9.2972403	28.6144838	SERTAD3	SERTA domain containing 3
26	39	ILMN_1775330	3.72E-17	9.2645566	28.4069667	C15orf52	chromosome 15 open reading frame 52
27	43	ILMN_1773307	4.3E-17	-9.2423297	28.2659998	NAP1L5	nucleosome assembly protein 1 like 5
28	44	ILMN_3272378	4.3E-17	9.2421831	28.26507	EZR	ezrin
	46	ILMN_1716552	4.72E-17	9.2279875	28.175107	ENAH	enabled homolog (Drosophila)
	47	ILMN_1689445	5.12E-17	9.2155059	28.0960491	POLR2H	RNA polymerase II subunit H
	52	ILMN_1709032	6.97E-17	9.1679191	27.7950133	FYCO1	FYVE and coiled-coil domain containing 1
	53	ILMN_2058070	7.23E-17	-9.1622555	27.7592254	NEDD8	neural precursor cell expressed, developmentally down-regulated 8
	54	ILMN_1692962	7.24E-17	9.161975	27.7574526	CTDSP2	CTD small phosphatase 2
	55	ILMN_1795937	7.32E-17	9.1603245	27.7470249	EZR	ezrin
	56	ILMN_2103720	8.02E-17	-9.1461619	27.6575766	MRPL15	mitochondrial ribosomal protein L15
	62	ILMN_1810559	1.21E-16	9.0829873	27.2592339	RHOQ	ras homolog family member Q
	65	ILMN_1718734	1.49E-16	9.0505732	27.0552703	MLLT6	MLLT6, PHD finger domain containing
	70	ILMN_2152581	1.77E-16	9.023388	26.8844332	STK38	serine/threonine kinase 38
	71	ILMN_1718769	1.89E-16	9.0130922	26.8197857	ITSN1	intersectin 1
	72	ILMN_1700144	2.02E-16	9.0030372	26.7566786	ITGA10	integrin subunit alpha 10
	79	ILMN_2038775	2.37E-16	-8.9781879	26.6008418	TUBB2A	tubulin beta 2A class IIa

Table 2: A set of 84 genes differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease (1/2).

The rank of differential expression, the transcript ID, the p-value of differential expression, t, a moderated t-statistic, B, the log-odds of differential expression, and the gene name are listed in this chart, from GSE132903.

81	ILMN_1778382	2.81E-16	-8.9516186	26.4344102	C17orf102	chromosome 17 open reading frame 102
83	ILMN_3239181	2.9E-16	8.9469216	26.4050091	ITPRIP	inositol 1,4,5-trisphosphate receptor interacting protein
87	ILMN_1798485	3.51E-16	-8.9169196	26.2173565	ATP6V1E1	ATPase H+ transporting V1 subunit E1
93	ILMN_2363489	4.99E-16	-8.8618689	25.8737066	BRE	brain and reproductive organ-expressed (TNFRSF1A modulator)
95	ILMN_1755737	5.05E-16	8.860091	25.862623	TRABD	TraB domain containing
98	ILMN_1665554	5.9E-16	-8.8357145	25.7107483	BRF2	BRF2, RNA polymerase III transcription initiation factor 50 kDa subunit
99	ILMN_1757497	6.27E-16	-8.8262161	25.6516171	VGF	VGF nerve growth factor inducible
102	ILMN_1661500	6.46E-16	8.8213783	25.6215104	B4GALT4	beta-1,4-galactosyltransferase 4
105	ILMN_2364376	8.06E-16	8.7867005	25.4059037	ILK	integrin linked kinase
108	ILMN_1725666	8.38E-16	-8.78063	25.3681977	GTF2H3	general transcription factor IIH subunit 3
111	ILMN_1677376	9.91E-16	8.7542364	25.2043855	CHD7	chromodomain helicase DNA binding protein 7
113	ILMN_1796595	1.02E-15	-8.7494664	25.174803	C5orf22	chromosome 5 open reading frame 22
123	ILMN_1716089	1.42E-15	8.6975188	24.8530787	KANK2	KN motif and ankyrin repeat domains 2
124	ILMN_3242330	1.43E-15	8.6965692	24.8472055	FAM65C	family with sequence similarity 65 member C
134	ILMN_1745954	2.07E-15	8.6378943	24.4848282	CORO1C	coronin 1C
141	ILMN_1815086	2.88E-15	8.5856143	24.1628484	NINJ1	ninjurin 1
142	ILMN_1682034	2.9E-15	8.5848832	24.1583518	HEY2	hes related family bHLH transcription factor with YRPW motif 2
149	ILMN_1757552	3.47E-15	8.5564295	23.9834807	PTRF	polymerase I and transcript release factor
151	ILMN_1805192	3.88E-15	8.5385018	23.8734326	ITPRIP	inositol 1,4,5-trisphosphate receptor interacting protein
152	ILMN_1753312	4.11E-15	8.5294207	23.8177283	PLXDC2	plexin domain containing 2
155	ILMN_1806733	4.48E-15	8.515454	23.7321069	COL18A1	collagen type XVIII alpha 1 chain
156	ILMN_1687743	4.67E-15	8.508929	23.6921272	BTBD7	BTB domain containing 7
157	ILMN_1678546	4.75E-15	-8.5062243	23.675559	PEX11B	peroxisomal biogenesis factor 11 beta
159	ILMN_1723969	5.16E-15	-8.492995	23.5945556	PLCB1	phospholipase C beta 1
160	ILMN_2405642	5.19E-15	-8.4921831	23.5895864	DHDDS	dehydrodolichyl diphosphate synthase subunit
161	ILMN_2081813	5.22E-15	-8.4913779	23.5846576	PCSK1	proprotein convertase subtilisin/kexin type 1
162	ILMN_1815057	5.34E-15	8.4876896	23.5620863	PDGFRB	platelet derived growth factor receptor beta
169	ILMN_1744212	8.1E-15	8.4210843	23.15524	INPP5D	inositol polyphosphate-5-phosphatase D
175	ILMN_2226628	9.64E-15	-8.3933762	22.9864206	ZNF184	zinc finger protein 184
176	ILMN_1760088	1E-14	-8.3869784	22.9474763	CCKBR	cholecystokinin B receptor
177	ILMN_2120695	1.01E-14	-8.3853563	22.9376046	TSPAN7	tetraspanin 7
178	ILMN_1781400	1.06E-14	8.3779139	22.8923228	SLC7A2	solute carrier family 7 member 2
190	ILMN_1681679	1.32E-14	8.3427914	22.678879	TSPO	translocator protein
194	ILMN_2197946	1.46E-14	-8.3271129	22.5837328	SCG3	secretogranin III
200	ILMN_1726743	1.71E-14	-8.3015782	22.4289525	MRPS30	mitochondrial ribosomal protein S30
201	ILMN_1811264	1.79E-14	-8.2942695	22.3846908	C15orf57	chromosome 15 open reading frame 57
214	ILMN_2316236	2.57E-14	-8.2354674	22.0292544	HOPX	HOP homeobox
221	ILMN_1739812	3.04E-14	-8.208284	21.8653461	PRKCG	protein kinase C gamma
227	ILMN_1700432	3.67E-14	8.1779662	21.6828433	ITPKB	inositol-trisphosphate 3-kinase B
234	ILMN_1787813	4.24E-14	8.1544902	21.5417481	SLC5A3	solute carrier family 5 member 3
242	ILMN_1788538	5.03E-14	-8.1268697	21.3759946	NCALD	neurocalcin delta
246	ILMN_1807919	5.41E-14	8.1152032	21.3060646	TNS1	tensin 1
249	ILMN_1673518	5.76E-14	-8.1048706	21.2441705	BRWD1	bromodomain and WD repeat domain containing 1

Table 2: A set of 84 genes differentially expressed in the middle temporal gyrus of patients with Alzheimer's Disease (2/2).