Differential Gene Expression in Alzheimer Disease - A study to find novel drug targets.

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Abstract:

Neurological disorders brings dangerous outcome to a person affecting with these kinds of disorders. It makes the quality of life equivalent to death. Alzheimer Disease is one of them. It is a devastating neurodegenerative disease. In this present work, I tried to find the Differential gene expression in various stages of Alzheimer Disease. I focused on the microarray data of four samples of Alzheimer Disease to find the disturbed cell signaling. This work presents the molecular insight into the disease. I discovered the similar gene expression pattern in other dangerous diseases. By looking into the pathway of all significant differentially expressed genes, I found the most potent drug target.

Keywords: Alzheimer Disease, cell signaling, Gene expression, Microarray, Samples, Pathways, Differential gene expression, Drug Target.

Introduction:

Several millions of peoples worldwide are affected by this devastating disease i.e., Alzheimer Disease (AD). The hallmark of AD brain includes the presence of amyloid plaques, neurofibrillary tangles, loss of neurons and synapses, and oxidative damage. We know that Mitochondrial dysfunction is linked to production of Reactive Oxygen Species (ROS) which leads to apoptotic pathway that results in neurodegenration. Another organelle affected is Endoplasmic reticulum (ER) that results in unfolding protein response (UPR). UPR is also connected with neurodegeneration if the repair machinery fails to improve the misfolded protein. Mitochondria are closely associated with ER, and the deleterious crosstalk between both organelles has been shown to be involved in neuronal degeneration in AD. The natural antioxidant gets suppressed if ROS is generated in excess that results in chronic oxidative stress.
In this paper I tried to find genes that are associated with all the above mentioned Biological process with their expression value in Alzheimer Disease. The expression value of top 10 ranked genes were compared with every samples present in Gene Expression Omnibus (GEO) database in order to find similar expression pattern in other diseases. Pathway analysis and GO process, function and localization were checked to find the potent drug target for Alzheimer Disease (AD).

Material and Methodology:

Microarray dataset selection:
I used Gene expression dataset entitled “Microarray analyses of laser-captured hippocampus reveal distinct gray and white matter signatures associated with incipient Alzheimer’s disease” from NCBI GEO [1], accession number is GSE28146.

Define gene grouping:
I assigned four groups of samples namely control, incipient, moderate and severe. There were 30 samples. In control group there were 8 samples. Likewise in incipient, moderate and severe, there were 7, 8 and 7 samples respectively.

Analyze differential gene expression among various defined groups:
I used GEO2R [2], an online tool in GEO database that compare two or more groups of Samples for identification of genes that are differentially expressed across experimental conditions. This tool extracts top 250 genes which are differentially expressed in all the four samples. Smaller the P-value, More reliable the data be. F-test combines the t-statistics for all the pair-wise comparisons into an overall test of significance for that gene. In case of two sample groups, B test is used to access the differential expression whereas F-test is used to access the differential expression when the number of samples is more than two.

Analyze the Expression similarity in various other molecular processes:
On the basis of adjusted P-value and F test, I took top ten differentially expressed genes for further analysis in ExpressionBLAST [3]. This tool compares our expression results to all the studies present in GEO database. Aim of this tool is to provide similar (or opposite) expression patterns to your results.

In Heatmap, three color is read as below

Green color: underexpressed. (-ve value)
Define pathways of significant deregulated differential genes:

Pathways analysis was found out from Unified GeneCards pathways database [4]. I proposed the disturbed cell signaling in Alzheimer disease on comparison with control samples.

Propose potent drug target:

On the basis of function and importance of identified differential genes, I proposed the potent drug target.

Results:

Comparison among control, incipient, moderate and severe stages in term of their samples results in various highly expressed genes using GEO2R. Top 10 highly expressed genes with their Rank, P-value, F value and GO terms are presented in Table 1.

Table1: Top ranked differentially expressed genes in Alzheimer Disease

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<td>microtubule motor activity</td>
<td>kinesin complex</td>
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<td>cellular metabolic process</td>
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<td>[pyruvate]</td>
<td>mitochondrial</td>
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<td>Gene</td>
<td>Entrez ID</td>
<td>FDR</td>
<td>Log2 Fold Change</td>
<td>Gene Product</td>
<td>Protein Function</td>
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<td>dehydrogenase (lipoamide) phosphatase activity matrix</td>
<td>3802794</td>
<td>0.424</td>
<td>10.71</td>
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<td>PDP2</td>
<td>1191579</td>
<td>0.424</td>
<td>10.58</td>
<td>magnesium-dependent protein serine threonine dephosphorylation phosphatase activity</td>
<td>pyruvate metabolic process threonine phosphatase activity metal ion binding regulation of acetyl-CoA biosynthetic process from pyruvate small molecule metabolic process Rab GTPase activator activity integral to membrane</td>
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<td>TBC1D9B</td>
<td>1043883</td>
<td>0.424</td>
<td>10.5</td>
<td>calcium ion binding carbohydrate metabolic process alpha-N-acetylgalactosamine alpha-2,8-sialyltransferase activity protein serine dephosphorylation</td>
<td>integral to membrane integral to membrane integral to Golgi membrane</td>
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<td>ST8SIA1</td>
<td>2265835</td>
<td>0.45</td>
<td>10.15</td>
<td>sialyltransferase activity cellular response to heat glycosphingolipid biosynthetic</td>
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<td>process</td>
<td>positive regulation of cell proliferation</td>
<td>protein glycosylation</td>
<td>calcium-dependent cysteine-type endopeptidase activity</td>
<td>Proteolysis</td>
<td>intracellular</td>
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<td>SOLH</td>
<td>5362150</td>
<td>0.45</td>
<td>10.02</td>
<td>cysteine-type peptidase activity</td>
<td>regulation of transcription, DNA-dependent</td>
<td>intracellular</td>
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<td>peptidase activity</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>sequence-specific DNA binding transcription factor activity</td>
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<td></td>
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<td></td>
<td>zinc ion binding</td>
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</tbody>
</table>

In this Heatmap (Fig 1) 0 indicates input and 1-25 indicates samples expression with significant match with our input.
Fig 1: Heatmap showing the similar expression pattern with Alzheimer Disease highly expressed genes.

In ExpressionBLAST we found 25 significant samples matching with our expression data on Alzheimer diseases. These samples are related to many cancers like breast, prostate, gastric, colon, bladder, melanoma, then autoimmune disorders, cardiomyopathy, inflammation, stroke and infections.

Table 2: Similar Expression patterns in various other diseases.

<table>
<thead>
<tr>
<th>Expression Similarity Ranking</th>
<th>GEO Samples</th>
<th>P-value</th>
<th>Samples Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GSE21921</td>
<td>0.0001</td>
<td>GSM description:Gene Expression Profiling of Formalin Fixed Paraffin Embedded Familial Breast Tumours Using the Whole Genome DASL Assay&lt;br&gt;&lt;br&gt;&lt;strong&gt;Conditions:&lt;/strong&gt;51297 4690176038 a vs 40339 4846417040 h&lt;br&gt;&lt;br&gt;&lt;strong&gt;PMID:&lt;/strong&gt;20593485;</td>
</tr>
<tr>
<td>2</td>
<td>GSE24891</td>
<td>0.0001</td>
<td>GSM description:Transcriptomic fingerprints in human peripheral blood mononuclear cells indicative of genotoxic and non genotoxic carcinogenic exposure&lt;br&gt;&lt;br&gt;&lt;strong&gt;Conditions:&lt;/strong&gt;phip 25 m sample 4 23877d vs etoh 05 sample 4 12993b&lt;br&gt;&lt;br&gt;&lt;strong&gt;PMID:&lt;/strong&gt;</td>
</tr>
<tr>
<td></td>
<td>GSE</td>
<td>p-value</td>
<td>GSM description</td>
</tr>
<tr>
<td>---</td>
<td>--------</td>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>3</td>
<td>GSE17755</td>
<td>0.0001</td>
<td>Human peripheral blood cells autoimmune diseases vs healthy individuals</td>
</tr>
<tr>
<td>4</td>
<td>GSE12046</td>
<td>0.0003</td>
<td>Expression profiles and ChIP on chip genomewide experiments with R2G mutant virus</td>
</tr>
<tr>
<td>5</td>
<td>GSE24796</td>
<td>0.0005</td>
<td>Effects of Genistein on LNCaP Gene Expression</td>
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<tr>
<td>6</td>
<td>GSE12928</td>
<td>0.0005</td>
<td>NMD inhibition fails to identify tumour suppressor genes in microsatellite stable gastric cancer cell lines</td>
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<tr>
<td>7</td>
<td>GSE37119</td>
<td>0.0005</td>
<td>Identification of target genes of cancer related microRNAs in human cancer</td>
</tr>
<tr>
<td>8</td>
<td>GSE12428</td>
<td>0.0011</td>
<td>Current smoking specific gene expression signature in bronchial epithelium is enhanced in squamous cell lung cancer</td>
</tr>
<tr>
<td>9</td>
<td>GSE22209</td>
<td>0.0017</td>
<td>Reduced seed region based off target activity with lentivirus mediated RNAi</td>
</tr>
<tr>
<td>10</td>
<td>GSE33651</td>
<td>0.002</td>
<td>Genome wide gene expression profile of human gastric cancer</td>
</tr>
<tr>
<td></td>
<td>GSE</td>
<td>p-value</td>
<td>GSM description</td>
</tr>
<tr>
<td>----</td>
<td>---------</td>
<td>---------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>11</td>
<td>GSE9800</td>
<td>0.0021</td>
<td><strong>GSM description:</strong> Expression signature of cardiac muscle as a potential diagnostic or prognostic tool for dilated cardiomyopathy</td>
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<tr>
<td>12</td>
<td>GSE28475</td>
<td>0.0024</td>
<td><strong>GSM description:</strong> Genome wide Expression Assay Comparison Across Frozen and Fixed Postmortem Brain Tissue Samples</td>
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<tr>
<td>13</td>
<td>GSE15523</td>
<td>0.0029</td>
<td><strong>GSM description:</strong> A Core MYC Gene Expression Signature is prominent in basal like cancer</td>
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<tr>
<td>14</td>
<td>GSE28948</td>
<td>0.003</td>
<td><strong>GSM description:</strong> TMPRSS2 ERG HDACs and EZH2 are involved in an AR centric transcriptional circuitry that calibrates androgenic response for prostate cancer progression gene expression data</td>
</tr>
<tr>
<td>15</td>
<td>GSE38230</td>
<td>0.0031</td>
<td><strong>GSM description:</strong> SCC of the vulva</td>
</tr>
<tr>
<td>16</td>
<td>GSE7469</td>
<td>0.0031</td>
<td><strong>GSM description:</strong> Defective cell cycle checkpoint functions in melanoma are associated with altered patterns of gene expression</td>
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<tr>
<td>17</td>
<td>GSE763</td>
<td>0.0033</td>
<td><strong>GSM description:</strong> Cell type specific responses to chemotherapeutics in breast cancer</td>
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<tr>
<td>18</td>
<td>GSE11223</td>
<td>0.0046</td>
<td><strong>GSM description:</strong> Colon biopsies from UC patients and healthy controls</td>
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<tr>
<td>19</td>
<td>GSE12434</td>
<td>0.0048</td>
<td><strong>GSM description:</strong> Macrophage specific inhibition of NF B activation impairs foam cell survival</td>
</tr>
</tbody>
</table>
Super pathways of all differentially expressed genes are mentioned in Table 3

Table 3: Pathways of differentially expressed genes

<table>
<thead>
<tr>
<th>Differentially Expressed genes in Alzheimer</th>
<th>Pathways involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFB125</td>
<td>Beta defensins pathway</td>
</tr>
<tr>
<td></td>
<td>Immune System Pathway</td>
</tr>
<tr>
<td>TRIOBP</td>
<td>Actin modification.</td>
</tr>
<tr>
<td></td>
<td>Barbed-end actin filament capping.</td>
</tr>
<tr>
<td></td>
<td>Positive regulation of substrate adhesion-</td>
</tr>
<tr>
<td>Protein</td>
<td>Functions/Pathways</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------</td>
</tr>
</tbody>
</table>
| IL1B | PEDF Induced Signaling  
TGF-Beta Pathway  
Toll-like receptor signaling pathway  
Rho Family GTPases  
Immune response_Bacterial infections in normal airways |
| ZAN | Sweet Taste Signaling |
| PER4 | No pathway discovered for this protein |
| KLC3 | Immune System.  
Kinesins.  
MHC class II antigen presentation.  
Factors involved in megakaryocyte development and platelet production.  
Platelet activation, signaling and aggregation |
| PDP2 | Pyruvate metabolism.  
TCA Cycle.  
Metabolism.  
Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins |
| TBC1D9B | No pathway discovered for this protein |
| ST8SIA1 | Ganglio Sphingolipid Metabolism  
Glycosphingolipid biosynthesis - globo series.  
Glycosphingolipid biosynthesis - lacto and neolacto series.  
Metabolism |
| SOLH | No pathway discovered for this protein |

**Discussion:**

These results depict the following main points:

The first ranked **DEFB125** gene was found to be mostly affected in Alzheimer disease. It is the highly expressed gene in this disease. This protein is located in extracellular region. Its main function includes defense response to bacterium. Probably the initial cause is bacterial infections. Thereafter Immunity plays a vital role in microbial degradation.

The Second ranked **TRIOBP** gene was found to be mostly affected in Alzheimer disease. It is also the highly expressed gene in this disease. Its main function includes GTP-Rho binding, actin filament binding, myosin II binding, phospholipid binding, ubiquitin
protein ligase binding. It is localized in cytoplasm. It performs the following tasks: actin modification, barbed-end actin filament capping, cell division, mitosis, positive regulation of substrate adhesion-dependent cell spreading. It indicates disturbances in actin/myosin dynamics causes Alzheimer Diseases.

The Third ranked **IL1B** gene was found to be mostly affected in Alzheimer disease. It is the next highly expressed gene in this disease. This protein is localized in cytosol and extracellular. Its falls PEDF Induced Signaling, TGF-Beta Pathway, Toll-like receptor signaling pathway, Rho Family GTPases, Immune response Bacterial infections in normal airways. Disturbances in these signaling promote Alzheimer Disease.

The fourth ranked **ZAN** gene was found to be mostly affected in Alzheimer disease. It is the next highly expressed gene in this disease. This protein is localized in plasma membrane. Its main function is cell-cell adhesion and kinesin binding. This indicates disturbances in cell-cell adhesion and kinesin binding promote Alzheimer Disease.

The fifth ranked **PER4** gene was found to be mostly affected in Alzheimer disease. It is the next highly expressed gene in this disease. This protein is localized in ciliary rootlet. Its main function is axon cargo transport. This indicates disturbances in axon cargo transport promote Alzheimer Disease.

The sixth ranked **KLC3** gene was found to be mostly affected in Alzheimer disease. It is the next highly expressed gene in this disease. This protein is localized in cytoplasm and mitochondrial matrix. Its main functions are microtubule binding, microtubule motor activity, pyruvate dehydrogenase (lipoamide) phosphatase activity. This protein falls under Immune System, Kinesins, MHC class II antigen presentation, Factors involved in megakaryocyte development and platelet production, Platelet activation, signaling and aggregation. This indicates disturbances in immune system promote Alzheimer Disease.

The seventh ranked **PDP2** gene was found to be mostly affected in Alzheimer disease. It is the next highly expressed gene in this disease. This protein is localized in membrane. Its main functions are magnesium-dependent protein serine threonine phosphatase activity, metal ion binding, Rab GTPase activator activity. This protein falls under Pyruvate metabolism, TCA Cycle, Metabolism, Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins. This indicates disturbances in metabolism promote Alzheimer Disease. This clearly indicates cause and effect relationship between Diabetes and Alzheimer Diseases.
The eighth ranked TBC1D9B gene was found to be mostly affected in Alzheimer disease. It is the next highly expressed gene in this disease. This protein is localized in membrane and golgi membrane. Its main functions are calcium ion binding, alpha-N-acetylneuraminate alpha-2,8-sialyltransferase activity. This indicates disturbances in calcium signaling promote Alzheimer Disease. This clearly indicates cause and effect relationship between NMDA and Ryanodine receptor dysfunction and Alzheimer Diseases.

The ninth ranked ST8SIA1 gene was found to be mostly affected in Alzheimer disease. It is the next highly expressed gene in this disease. This protein is localized in membrane integral. Its main functions are sialyltransferase activity, calcium-dependent cysteine-type endopeptidase activity. Similar to TBC1D9B, this indicates disturbances in calcium signaling promote Alzheimer Disease. This clearly indicates cause and effect relationship between NMDA and Ryanodine receptor dysfunction and Alzheimer Diseases.

The tenth ranked SOLH gene was found to be mostly affected in Alzheimer disease. It is the next highly expressed gene in this disease. This protein is localized in intracellular. Its main functions are cysteine-type peptidase activity, peptidase activity, sequence-specific DNA binding transcription factor activity, zinc ion binding. This clearly indicates the inappropriate nicking and protein mis-folding and that results into aggregation.

**Conclusion:**

The main Biological process observed in this study are deregulated calcium signaling, actin-myosin impaired dynamics, immune disorders, metabolic disorders, increased activity of endopeptidases, protein misfolding and aggregation, cell-cell adhesion, cell spreading and the major signaling PEDF Induced Signaling, TGF-Beta Pathway, Toll-like receptor signaling pathway, Rho Family GTPases, Immune response Bacterial infections in normal airways. All these processes if impaired are the source of Alzheimer Diseases. But if we see the Heatmap, we will come to know that KLC3 gene is highly expressed in many samples as compared to other genes in our study and it is involved in microtubule binding, microtubule motor activity, pyruvate dehydrogenase (lipoamide) phosphatase activity. If we target this gene for Alzheimer treatment, most of the above mentioned impaired signal will come under control. Out of ten differentially expressed genes in Alzheimer disease, KLC3 is most appropriate drug target for treating Alzheimer and many other diseases like immune related disorders.
References:


3- ExpressionBLAST: http://www.expression.cs.cmu.edu/index.html