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KAZN/KIAA1026 Gene Is Upregulated in Three Neurodegenerative Diseases

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Abstract: Neurodegenerative diseases are incurable conditions that occur in the central nervous system and are characterized by a progressive death of neural cells with multiple known and unknown causes. The three that were analyzed in this study were Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis. Gene expression data from 59 post-mortem brain samples out of an extensive cohort of 113 patients from the NCBI GEO Database provided the basis for this gene expression comparison. The NCBI GEO2R tool was used to find the genes with significant differential expression and accordingly identified 19 such genes at $p<0.05$, with 4 of them being commonly upregulated: KAZN/KIAA1026, PLA2G7, ALOX15B, and PLEKHM1. String™, an online gene interaction database on the public domain, was used to map out any possible connections between them. Although no straightforward interactions/connections were found with String™, KAZN was identified in previous studies to have an interaction with an ataxia-causing protein. Furthermore, some isoforms of KAZN are known to interact with microtubules, a cytoskeletal component known to lead to neurodegeneration when dysfunctional. This gene may provide further insight into the pathogenesis of neurodegenerative diseases and act as a potential therapeutic target due to its potential role in the dysfunction of the neural cytoskeleton and its already established place in the protein-protein interaction network of ataxia-causing diseases.

Keywords: Neurodegenerative Diseases, Gene Expression, Therapeutic Target, KAZN/KIAA1026 Gene, NCBI GEO Database, NCBI GEO2R, String

1. Introduction

Neurodegenerative diseases are incurable conditions resulting from the progressive degeneration and death of nerve cells within the central nervous system. Parkinson's Disease (PD), Alzheimer's Disease (AD), and Amyotrophic Lateral Sclerosis (ALS) all result from defective or dysfunctional neural populations [1]. Cellular and molecular pathological changes in certain areas of the brain and spinal cord lead to this neural loss. Several neurodegenerative diseases share common features such as mitochondrial energy deficits and abnormal cell transport that suggest a correlation among pathways of neurodegeneration, despite large clinical differences. Evidence suggests that glial support systems including myelin sheaths are not retained across neurodegenerative disease as well [2]. ALS is caused by the degeneration of upper and lower motor neurons in the spinal cord, brainstem, and motor cortex and has no exact known cause. Parkinson's disease, like many neurodegenerative diseases, also results from motor neuron death in the absence of dopamine within the substantia nigra. The accumulation of beta amyloid protein which blocks signaling and communication between neurons and tau protein tangles are known to contribute to Alzheimer's disease [3].

Approximately 50 million Americans are affected with a neurological disorder each year as the nation's population progressively ages. These disorders cost billions of dollars each year in health care costs and $100 billion is estimated to be spent on solely Alzheimer's disease. The exact pathogenesis of ALS, AD, and PD is largely unknown which makes targeted treatment difficult, if not impossible [4]. None of the currently available drugs for neurodegenerative diseases have the ability to inhibit progressive neuronal dysfunction and the subsequent disabilities, although they help alleviate symptoms and comfort patients [2]. Central Nervous System (CNS) drugs are being developed over a prolonged period of time, and research of the underlying pathogenesis of these diseases is paramount to enhancing

treatment methods to target specific genetic biomarkers [2]. Current therapeutic strategies attempting to rescue, replace, and regenerate damaged neurons may be rendered ineffective by the lack of knowledge regarding the genetic pathology of these diseases [5]. In addition, few studies have conducted a cross-disease approach with gene expression profiling for neurodegenerative diseases [2].

Despite all of this, some key molecules playing a role in neurodegeneration in both pro-apoptotic and neuroprotective signaling pathways have been identified thanks to the utilization of proteomics and transcriptomics in recent years [2]. Dysregulation of certain genes, such as dynactin-1 in ALS or osteopontin in MS, have been identified by gene expression profiling as potential causative agents in several neurodegenerative diseases. Genes related to the function of mitochondria have been pointed out as having involvement across the board of neurodegenerative disorders. Being the main regulators of cell death, dysregulation in mitochondrial genes is likely a factor in disease pathogenesis. It is hypothesized that many neurodegenerative disorders, including Parkinson's and Alzheimer's, may have a common pathogenesis involving the translation of misfolded amyloid proteins which aggregates and deposits within the central nervous system [7]. Although most of the cases of protein aggregation occurs early on and is sporadic, mutations in the transcribed genes for amyloid proteins raise the chances of misfolding and subsequent aggregation. As a common motif in neurodegenerative disease, targeting the expression levels of mutated genes opens the door to potential treatment across the spectrum of neurodegenerative diseases [7].

Presence of a neurodegenerative disease almost always indicates some type of neuron damage or death has occurred within the central nervous system [1]. ALS, Parkinson's, and Alzheimer's are all known to share common characteristics both in their pathogenesis as well as clinically, although many remain undiscovered [8]. Understanding features of any one of the three tested diseases may lead to discoveries of important aspects necessary for treatment of the other two. A common scenario in all neurodegenerative diseases are neurons highly susceptible to stress, which may be caused by environmental toxins. Oftentimes, the upregulation of protein misfolding and downregulation of protein recycling leads to neural loss as toxic proteins spread from one neuron to another. Multiple Sclerosis (MS) in particular often results from an autoimmune response which causes inflammation in neurons [8]. Alzheimer's disease is a very insidious and progressive disease that occurs at a later stage in life and distinguishes itself from other neurodegenerative diseases with its tendency for global cognitive decline and accumulation of Aβ proteins within the brain. Memory loss and loss of mental function is most commonly associated with AD [9]. Clinically distinguishing Parkinson's disease from that of Alzheimer's is the presence of a progressive motor neuron loss leading to a movement disability entailing the triad of tremor, bradykinesia, and rigidity. It also has an onset earlier than that of AD, occurring between the ages of 50 and 60. Similarly to PD, ALS tends to affect motor neurons in the brain and spinal cord, causing a loss of movement control and an early death [9].

In 2015, Durrenberger and his colleagues collected genome-wide expression data for six common neurodegenerative diseases and analyzed whole-genome expression patterns for commonalities in gene dysregulation that could be occurring across a spectrum of neurodegenerative diseases [2]. One important objective in conducting this study was to possibly find common molecular pathogenic mechanisms in neurodegeneration. Within the selection criteria, no dysregulated gene was identified as common to all six diseases that were studied. When comparing 4 or 5 diseases, it was found that there were 61 genes in dysregulation. The genes that were identified are mostly related to neural homeostatic, survival, and synaptic plasticity pathways, in addition to some inflammatory response genes [2]. In 2007, Grunblatt and her colleagues compared the analysis of gene expression patterns between Alzheimer's and Parkinson's [10]. They profiled the gene expression data for AD and PD to use them in the comparison and then age matched control patients with brain tissue samples from the hippocampus, gyrusfrontalis-medius, and the cerebellum with a Gene-Chip microarray. Twelve genes were commonly dysregulated in both AD and PD, while four genes were found to show different expression profiles between diseases dependent upon the region of the brain. Many of these dysregulated genes identified play a key role in oxidative stress, the insulin system, protein transport, and signal transduction pathways within the central nervous system (CNS) [10].

Many genetic factors for neurodegenerative diseases remain undiscovered and targeted treatment methods are faulty due to a lack of understanding of the pathogenesis of these diseases. The purpose of this study was to analyze and identify the key genes which are dysregulated in the pathogenesis of neurodegenerative diseases including Parkinson's, Alzheimer's, and ALS in the hopes of creating treatment methods for the vast spectrum of diseases of this type which exist. There are likely dysregulated genes common to Parkinson's, Alzheimer's, and ALS which play a role in the overall neurodegenerative pathogenesis. Studies point to a common pathogenesis in neurodegenerative diseases involving the aggregation of misfolded amyloid proteins within the central nervous system [7]. Mutations in the respective amyloid genes are suggested as being a factor in this process [7].

2. Methods

This experiment utilized NCBI GEO DataSet GSE26927 which contains genome-wide expression data from 113 patients' brain tissue samples spread among 6 neurodegenerative disease groups and 6 control groups. The creators of the data set prepared the RNA samples for microarray genome analysis using the Illumina TotalPrep™-96 RNA Amplification Kit. BeadChips were then scanned with the Illumina BeadArray while also following the

standard Illumina scan protocol [2]. The data set was trimmed to include only patient genomes pertaining to Alzheimer's, Parkinson's, and ALS as well as their respective control groups. The 250 most significantly dysregulated genes sorted by p-value of differential expression were separated into upregulated and downregulated groups using R statistics through a T-test. The biological connections between dysregulated genes were mapped using String, an online gene interaction viewer. Genes with p-values <0.05 were selected as statistically significant enough to be included in the cross-disease comparison. Once the commonly dysregulated genes for each disease were compiled together, they were manually compared to each other in an Excel spreadsheet to each other in order to assemble a list of genes which are found to be dysregulated across the spectrum of the studied neurodegenerative diseases. A string identifier add-on from AbleBits™ assisted in the process. The functions and connections of these genes were then mapped out using String in order to assist in drawing conclusions about the relation between these dysregulated genes and the pathogenesis of neurodegenerative diseases. A search through the literature for potential gene connections was also conducted to identify any other key interactions with the pathogenesis of neurodegeneration.

3. Results

The analysis of the genetic expression data for 59 total patients yielded a total of 19 commonly dysregulated genes among all 3 neurodegenerative diseases. Table 1 shows each of these 19 genes along with their corresponding logFC sign. A positive LogFC sign indicates gene upregulation while a negative LogFC value indicates gene downregulation. All p values for the differences in genetic expression were less than 0.05. The data values are arranged for Alzheimer's, Parkinson's, and ALS, respectively.

Table 1. *Commonly Dysregulated Genes.*

Gene Name	LogFC AD	LogFC PD	LogFC ALS
KAZN/KIAA1026	+	+	+
ALOX15B	+	+	+
PLA2G7	+	+	+
NR2C2	+	+	--
GAS1	+	--	--
LY6G5C	+	--	+
GSN	--	+	--
B4GALT1	+	--	+
HSP90AA1	--	+	--
RPS6KA5	+	--	--
VWA5A	--	+	+
PIP5K1B	--	+	+
TMEM159	--	+	+
FKBP2	--	+	--
UHMK1	--	+	+
HMGA1	--	--	+
SMYD1	+	--	--
PLEKHM1	+	+	+

Most of the genes identified had varying functions with respect to their molecular pathways, although a fair number were noted to be related to protein folding and maintenance. Through manual comparison of logFC values for individual genes in each disease, it was found that 4 genes were commonly upregulated while none were found to be commonly downregulated. The expression data included multiple transcript variants for some of the same genes, in which case any variant was used to make conclusions about commonalities in upregulation and downregulation. By default, multiple genes were found to be dysregulated in the same fashion for any 2 of the 3 diseases. Figures 1-3 show the upregulation of KAZN, one of the four commonly upregulated genes, in graphical format for the patients with Alzheimer's, Parkinson's, and ALS, respectively.

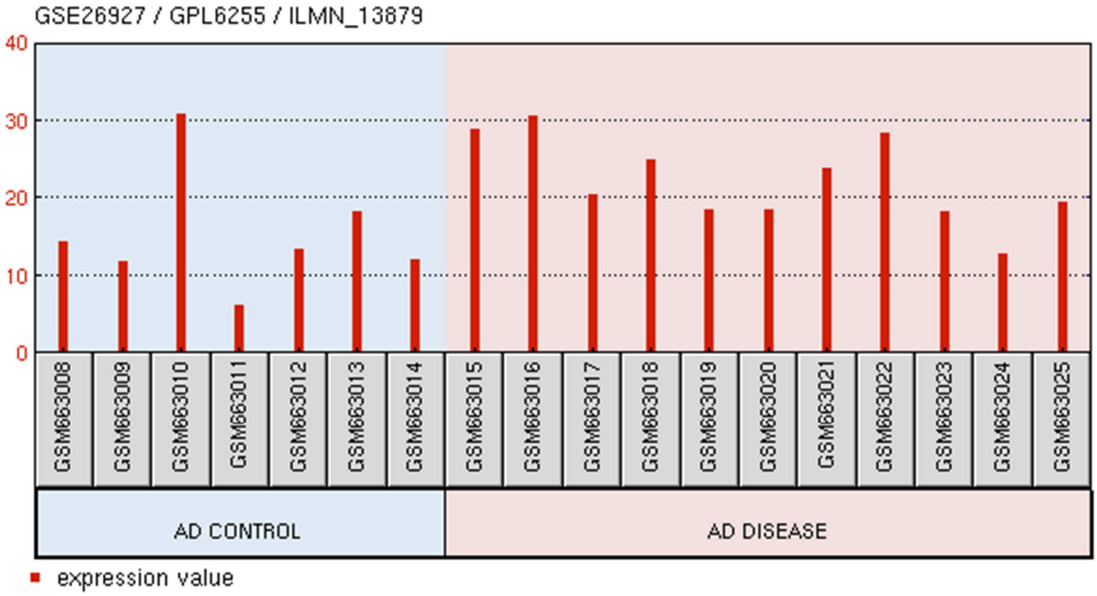

Figure 1. *Graph showing expression level of KAZN gene in Alzheimer's.*

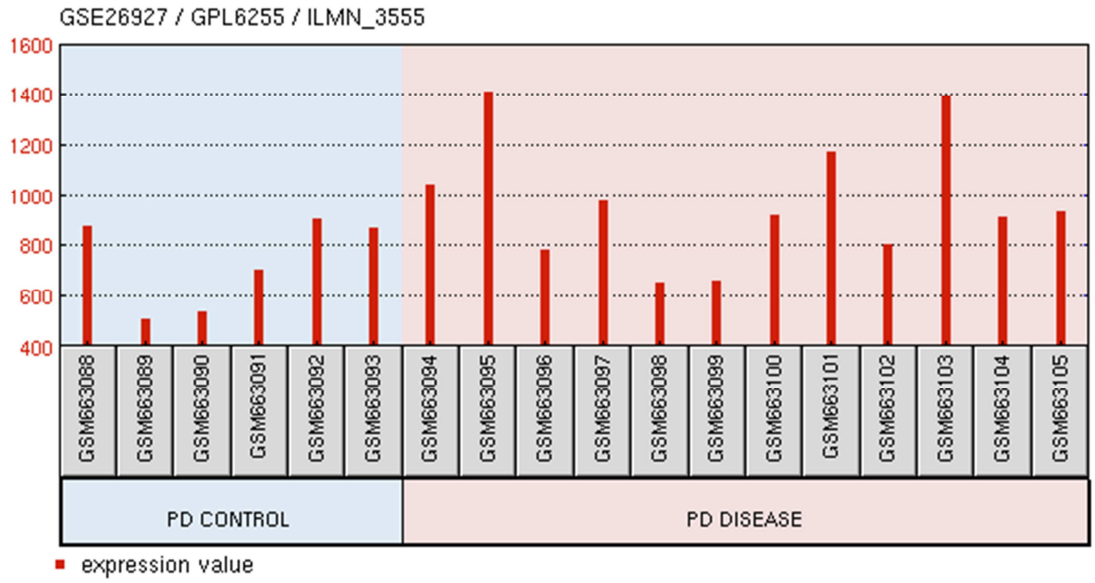

Figure 2. *Graph showing expression level of KAZN gene in Parkinson's.*

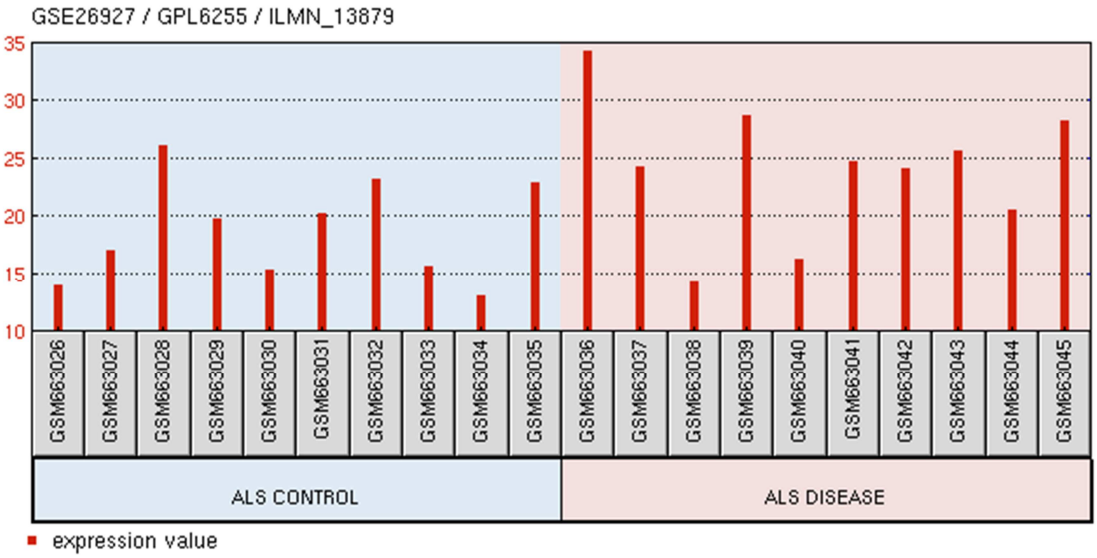

Figure 3. *Graph showing expression level of KAZN gene in ALS.*

The interactions and molecular pathways between the 4 upregulated genes were mapped out utilizing the String™ database and online platform. Figure 4 below shows the supposed lack of association between these genes.

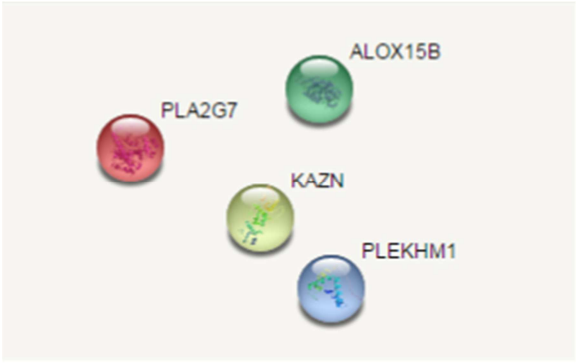

Figure 4. *Functional protein association network for 4 upregulated genes.*

Although no experimentally determined connections between the genes were found, there is the possibility that a molecular pathway involving PLA2G7, ALOX15B, KAZN, and PLEKHM1 which determines the pathogenesis of neurodegenerative diseases could be identified and further research must follow to pursue this objective. The experiment explicitly supports the hypothesis to the extent that there were commonly dysregulated genes in all 3 neurodegenerative diseases. KAZN, also commonly known as KIAA1026, was the only gene found in the literature to be in an interaction with a known neurodegeneration-causing pathway [11].

4. Discussion

The 4 genes found to be commonly upregulated support the first component of the hypothesis that in all of the 3

neurodegenerative diseases selected for the study there would be commonly dysregulated genes. The increase in gene expression (and likely protein production) as opposed to a decrease is favorable for the hypothesis as neurodegeneration is known to be the product of surplus proteins in the brain. All of the genes have varying functions from vesicular transport in the osteoclast to modulating the action of platelet-activating factors in the blood. One of the upregulated genes, KAZN, is a periplakin-interacting protein which has been studied in various past experiments in relation to Parkinson's disease and ataxias. It was found by Lim and his colleagues in 2006 that this gene interacts with another coil gene known to cause certain ataxias and is thus part of a larger protein-protein interaction network involving the molecular pathways in Purkinje cell degeneration [11]. Purkinje cells are responsible for motor coordination and when they degenerate it can cause numerous kinds of movement disorders such as sporadic Parkinson's disease or Ataxia-telangiectasia. It has been noted that some isoforms of KAZN are also known to associate with microtubules. With respect to the cytoskeletal functioning of neural cells, research has pointed to reduced microtubule stability as being observed in several related neurodegenerative diseases including Alzheimer's, Parkinson's, and ALS [12]. Hyperstable microtubules have also been identified as concurrent with neurodegeneration. Evidence from previous studies suggests that a causative link exists between the dysfunction of cytoskeletal components including microtubules which control neural processes such as synaptic signaling and the pathogenesis of neurodegeneration [13]. KAZN's upregulation in all 3 neurodegenerative diseases and its possible involvement in the molecular mechanisms underlying neurodegeneration implies that using methods of inhibiting gene expression such as histone deacetylation to restore KAZN to its normal level of expression may slow or stop the process of neurodegeneration within the central nervous system.

The internal validity of the experimental design is strengthened by the elimination of outlier data prior to analysis and the multiple replications of the experiment that increased accuracy and accounted for potential human error. An extensive cohort of subjects was analyzed and expression levels were carefully measured by Durrenberger et al. [2] using the Illumina™ BeadChip and Reader. Externally, the preliminary results suggest that certain methods of masking genetic expression could be used to help inhibit neurodegeneration if indeed these genes are part of a larger molecular pathway. This type of treatment might be generalized to all diseases involving degeneration of the central nervous system, given that the 3 diseases studied provides a proper representation of them.

5. Conclusions

Though the three neurodegenerative diseases analyzed differ greatly in their clinical features, it is evident that certain genetic factors play a direct role in the process of neural cell death. Commonalities in the neurodegenerative pathways among the three diseases which can be found in the literature validated this hypothesis and warranted the statistical comparison of expression levels between control and disease patients to discern the genetic pathways of the neurodegenerative pathogenesis. Microarray tests were able to show several genes that generate excess levels of mRNA in the brains of patients for all three diseases and yet only one gene, KAZN, implied a clear pathological connection. Graphical representations of exact expression levels in the patients show a fair amount of variation within groups, suggesting that a certain gene may play a more significant role in some patient's cognitive or motor deterioration than others. KAZN's isoforms' association with microtubules combined with its proven involvement in the degeneration of a GABAergic nerve cell located in the cerebellum is indicative of its possible interference (when overexpressed) with the normal functioning of the central nervous system in neurodegenerative diseases such as Alzheimer's, Parkinson's, and ALS. Microtubules in the cytoskeleton of the neural cell have a migratory role in transporting nutrients, organelles, and other materials essential to its own survival and there is the possibility that the overexpression of the protein isoforms coded by this gene which have found to be in interaction with this cytoskeletal component could directly or indirectly induce its destabilization through disaggregation [14]. Similar mechanisms of microtubular failure and eventual neural death have been observed with tau protein tangles in Alzheimer's disease [14]. It is crucial that the alteration of KAZN expression levels in the brain be conducted *in vivo* on organisms undergoing neurodegeneration in order to further validate its role in the neurodegenerative pathway. Future research may then involve creating a potential treatment for neurodegeneration which aims to inhibit the overexpression of KAZN utilizing the process of histone deacetylation or conducting the same computational procedure on diseases of the same type to discover other plausible genetic connections. The complete treatment plan could be tested on living organisms showing symptoms similar to what is observed in Alzheimer's, Parkinson's and ALS in order to gain insight into whether or not it could slow or stop the process of neurodegeneration within the CNS of humans.

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