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Bioinformatic Analysis of Alzheimer's Disease and Type2 Diabetes Mellitus: A Bioinformatic Approach

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Abstract

We evaluated the role of several proteins that are likely to be involved in alzheimers disease (AD) and type 2 diabetes mellitus (T2DM). By employing multiple sequence alignment using Clustalw tool, we have constructed a phylogenetic tree based on the functional protein sequences extracted form NCBI. The phylogram was constructed using neighbor joining algorithm. Our bioinformatic analysis reported that the two proteins such as AChE and BChE are playing major role in both the diseases out of ten common proteins between these two diseases. Our *in silico* study may pave way for new therapeutic interventions/biomarker identification in alzimers disease associated diabetes mellitus.

Keywords: Bioinformatics; type 2 diabetes mellitus; Alzheimer's disease

Introduction

Butyrylcholinesterase (BChE) is increased in the cerebral cortex of Alzheimer's disease (AD) patients, particularly those carrying å4 allele of the apolipoprotein E gene (ApoE) and certain BuChE variants that predict increased AD risk and poor response to anticholinesterase therapy. Darreh-Shori, et al(2006). Measured BChE activity and protein level in CSF of eighty mild AD patients in relation to age, gender, ApoE å4 genotype, cognition and cerebral glucose metabolism (CMRglc). BuChE activity was 23% higher in men than women ($p < 0.03$) and 40–60% higher in ApoE å4 negative patients than in those carrying one or two å4 alleles ($p < 0.0004$). CSF BuChE level correlated with cortical CMRglc. Patients with high to moderate CSF BuChE showed better cognitive function scores than others. They hypothesize that CSF BuChE varies inversely with BuChE in cortical amyloid plaques. Thus, low BuChE in a patient's CSF may predict extensive incorporation in neuritic plaques, increased neurotoxicity and greater central neurodegeneration.

Acetylcholinesterase and butyrylcholinesterase activities emerge in association with plaques and tangles in Alzheimer's disease. These pathological cholinesterases, with altered properties, are suggested to participate in formation of plaques (Mariam F. Eskander. et.al.2005). It is evident from the preceding discussion that acetylcholinesterase and butyrylcholinesterase are present in various regions of the brain and are increased in the brains of patients with Alzheimer's disease. Furthermore, the activities of these two enzymes seem to be closely associated with the disease activity itself. Thus, higher the activity of acetylcholinesterase and butyrylcholinesterase, more severe the manifestationsof Alzheimer's disease and increasing number of cortical and neocortical amyloid-rich neuritic plaques and neurofibrillary tangles(Guillozet A.et.al.1997, Greig NH.et.al.2005).

It is interesting to note that changes in the activities of acetylcholinesterase and butyrylcholinesterase have also

been reported in other diseases Acetylcholinesterase was found to be about an order of magnitude higher in islets of Langerhans than in the exocrine tissue in rat pancreas. This difference in activity was found in rats made diabetic with streptozotocin as well as in the controls (Godfrey DA .et.al.1975). Abbott et al (1993) reported that the activity of serum butyrylcholinesterase was significantly elevated in both type 1 (8.10 ± 3.35 units/ml) and type 2 (7.22 ± 1.95 units/ml) diabetes compared with the control subjects (4.23 ± 1.89 units/ml) ($P < 0.001$). In addition, serum butyrylcholinesterase activity correlated with serum fasting triacylglycerol concentration and insulin sensitivity in patients with type 1 and type 2 diabetes. On the other hand, in non-diabetic subjects with butyrylcholinesterase deficiency serum triacylglycerol levels were in the normal range. These results suggested that butyrylcholinesterase might have a role in the altered lipoprotein metabolism in hypertriglyceridaemia associated with insulin insensitivity or insulin deficiency in diabetes mellitus(Sanchez-Chavez G.et.al.2000).

In contrast, streptozotocin diabetes did not affect acetylcholinesterase activity in the retina but increased its activity in the cerebral cortex (100%) and in serum (55%), and decreased it by 30-40% in erythrocytes. The butyrylcholinesterase activity was decreased by 30-50% in retina and hippocampus and to a lesser extent in retinal pigment epithelium from rats treated with streptozotocin for one week. The changes noted in cholinesterase activities were not correlated with the fasting blood glucose concentration. These results suggest that diabetes might influence a specific subset of cells and isoforms of cholinesterases that could lead to alterations associated with diabetes complications (Sanchez-Chavez G.et.al.2001). It was also reported that the butyrylcholinesterase K variant allele was more common among Type II diabetic subjects than non-diabetic subjects suggesting that the close association of the butyrylcholinesterase gene (3q26) with Type II diabetes could be related to an identified susceptibility locus on chromosome 3q27 but independent of islet function(Sanchez-Chavez G.et.al.2001).

Sl.No	Gene name	Accession ID	Length	Tissue Type
1	ACHE	AAH94752	640 aa	Brain, hypothalamus
2	APOE	AAB59546	317 aa	liver and blood
3	BCHE	AAH08396.	64aa	Brain, primitive neuroectodermal
4	CETP	AAB59388	425aa	Liver
5	GAL	AAC09250	318aa	Blood
6	HGF	AAA52649	290aa	lambda gt10
7	IDE	AAA52712	1019aa	Hepatoma
8	MMP2	AAH02576	660aa	Brain, neuroblastoma
9	MMP9	AAH06093	707aa	Primary B-Cells from Tonsils
10	NGFB	AAI26151	241aa	Pooled, cerebellum, kidney, placenta,testis, lung, colon, liver, heart, thyroid, bladder,uterus,

Table 1: List of proteins Involved in AD and T2DM.

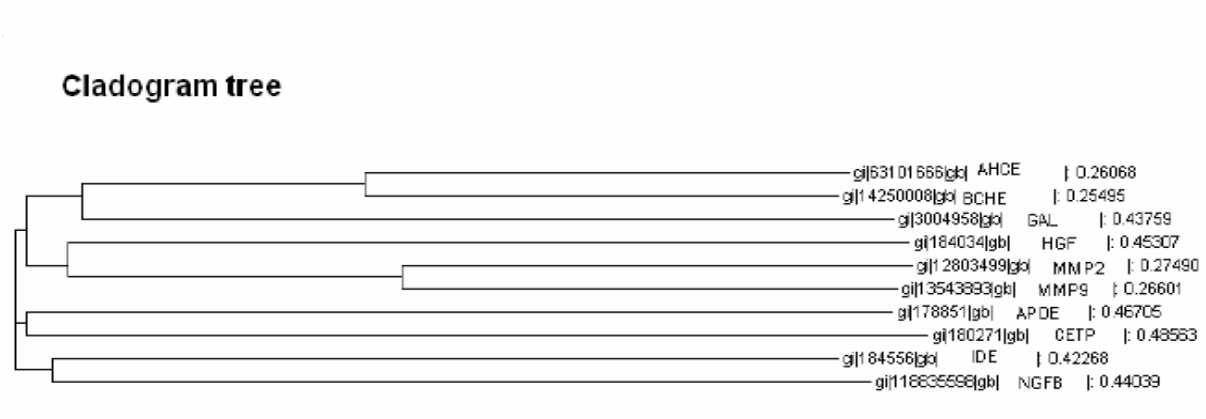

Figure 1: shows the relationship between the preoteins by using cladogram tree between Alzeimers and type 2 Diabetes.

Since elevated serum butyrylcholinesterase activity is elevated in the diabetic rat, mouse and humans, Dave and Katyare studied the source of the increased level of butyrylcholinesterase and reported that in alloxan- induced diabetic animals both the serum and cardiac butyrylcholinesterase activities were increased 2.2- to 2.8-fold with almost no significant change in the activity of the enzyme after insulin treatment compared with controls (Dave KR, Katyare SS.et.al.2002). Furthermore, correlation analysis showed that butyrylcholinesterase activity was positively correlated with age, sex, body mass index, hypertension and diabetes, as well as with triglycerides, total cholesterol, low-density lipoprotein cholesterol and apolipoprotein B (Apo B), whereas a step-wise multiple regression analysis revealed that the only risk factors for coronary heart disease that showed independent correlations with butyrylcholinesterase activity were, in descending order of importance, Apo B, triglycerides, and diabetes. These findings reinforce the idea that butyrylcholinesterase activity is associated with lipoprotein synthesis, hypertension, and diabetes (Alcantara VM .et.al.2002).

Above studies explains that AD and T2DM share several molecular processes that underlie the respective degenerative developments. In silico studies have established a pathway for in vivo/in vitro studies for identification of proteins, having therapeutic significance. Recent technological advances in genetics, genomics, proteomics, and bioinformatics offer great opportunities for biomarker discovery (Srinubabu et al, 2007). In the present study we have reported the common proteins involved in AD and T2DM.

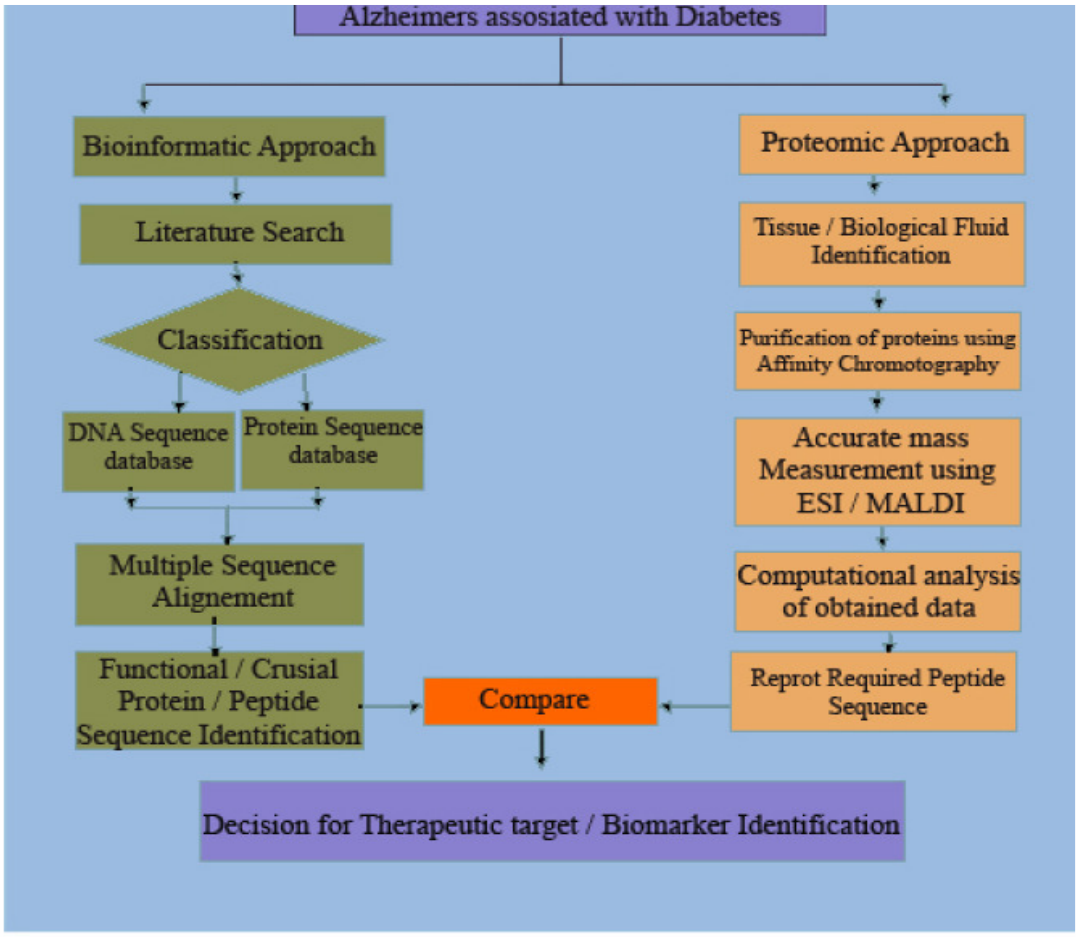

Figure 2: Schematic representation of the diabetic macrovascular complications with reference to bioinformatic and proteomic approaches for therapeutic drug target identification and/or biomarker identification

Material and methods

Based on the available literature we have collected 10 known proteins (table 1), which are believed to be involeved in pathogenesis of AD and T2DM. The functional protein sequence in FASTA forms for these genes are collected from NCBI (National Center for Biotechnology Information http://www.ncbi.nih.nlm.gov). These sequences are given to clustalw http://www.ebi.ac.uk/clustalw) for the multiple sequence alignment (it calculates that the best match for the selected sequences, and lines them up so that the identities, similarities and differences can be seen). Based on this result the score table and phylogeny tree are derived. The phylogeny shows the distance between the protein sequences. The protein sequences with minimum distance are AChE & BChE (figure 1).

Discussion

AD and T2DM are conditions that affect a large number of people in developed and developing countries. Both conditions are on the increase, and finding novel treatments to cure or prevent them are a major aim in research. Somewhat surprisingly, AD and T2DM share several molecular processes that underlie the respective degenerative developments. Tahirovic I et al (2007) performed the role of oxidative stress in the pathogenesis of metabolic diseases like diabetes mellitus and its complications, as well as in neurodegenerative disorders like AD and reported that the oxidative stress alterations in the brain of STZ-induced rats and humans with AD could be useful in the search for new drugs in the treatment of AD that have antioxidant activity. The misfolding of proteins plays an important role in both diseases, Our bioinformatic analysis hypothesize that the close distance association between AChE and BChE may modify the risk for AD in individuals with T2DM. In a similar *in silico* study conducted by Wang Y and Klemke RL, (2008), demonstrated that PhosphoBlast is a versatile mining tool capable of identifying related phosphorylation signatures and phosphoamino acid mutations among complex proteomics datasets in a highly efficient and accurate manner. Phosphoblast will aid in the informatics analysis of the phosphoproteome and the identification of phosphoprotein biomarkers of disease. So bioinformatic studies like multiple sequence alignment and Phosphoblast analysis will aid in the informatics analysis of the protein and the identification of new therapeutic interventions/ protein biomarkers of the disease.

Conclusions

While the identification of these candidate proteins involved in AD and T2DM is an important *in silico* milestone, follow up studies are required for validation in a larger population of individuals and for determination of laboratory-defined sensitivity and specificity values using novel proteomic and metabolomic tools. As represented in figure 2, the combination of proteomic and bioinformatic studies are useful for more accurate prediction of biomarkers/new therapeutic targets.

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