ROLE OF SYNUCLEIN BETA (SNCB) AND SYNUCLEIN GAMMA (SNCG) IN GLAUCOMA AND ALZHEIMER'S DISEASES – A BIOINFORMATIC APPROACH.

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ABSTRACT:

Glaucoma disease is deterioration of the optic nerve which slowly robs victims of their sight. Alzheimers is a slow death of brain cells that erodes memory and erases personality. Glaucoma is a chronic neurodegeneration of the optic nerve which affects the elder persons , so it has some similarity to Alzheimers since Alzheimers is also a disorder which affects elderly persons. In Glaucoma ,Optic nerves seem to accumulate the same amyloid beta protein that is the underlying cause of neuron death in the brains of Alzheimer's patients too.

The role of several proteins that are likely to be involved in Glaucoma and Alzheimers are been investigated by employing multiple sequence alignment method using ClustalW tool. Phylogram tree is been constructed using functional protein sequences extracted from NCBI. Phylogram is been constructed using Neighbour-Joining Algorithm in Bioinformatics approach.

Phylogram showed that Synuclein beta(SNCB) and Synuclein gamma (SNCG) plays a significant role in pathogenesis of Glaucoma and Alzheimers . It is likely that the proteins. such as GSTT1(glutathione S-transferase theta 1)and NPY (neuropeptide Y) also play a role in Glaucoma and Alzheimers next to SNCB and SNCG.

This bioinformatics approach of finding genes causing diseases would help in developing Drugs that inhibit or clear the bad amyloid protein which could prove to be useful in treating both these diseases.

KEYWORDS: CLUSTALW, Phylogram, Alzheimer's, Glaucoma, SNCB,SNCG.

1. INTRODUCTION

A major link between Alzheimers and Glaucoma has been discovered that could lead to the eye disease being regarded as an early stage of dementia.Eye's retina can provide a window in to the brain allowing doctors to diagnose Alzheimers by looking for nerve cell death.This knowledge means that the eye could also be used to test potential treatments for diseases like Alzheimers[1].

The rate of glaucoma among patients with Alzheimer's disease (AD) were found in 29 out of 112 patients with AD (25.9%).Patients with AD may have a significantly increased occurrence rate of glaucoma[2]. The stress caused during glaucoma causes the release of beta amyloid into the eye leading to nerve cell death. Nerve cell death is the cause of Alzheimers too. A rat glaucoma model revealed that raising the pressure on the eye caused, beta amyloid to be released which lead to nerve cell death[3].

The information is still scarce with regard to the involvement of various genes and proteins in causing Glaucoma and Alzheimers. The objective of the present study is to identify key protein(s) contributing to Glaucoma and Alzheimers using Bioinformatic Tools.

The genes of SNCB, SNCG , GSTT1, NPY have been hypothesized to play a role in Glaucoma and Alzheimers.Since the phylogram constructed using ClustalW showed that, the SNCG value is 0.11930 and SNCB value is 0.15159, lowest values among all the remaining gene values.

2. MATERIAL AND METHODS

We collected 26 known genes that are believed to be involved in the pathogenesis of Glaucoma and Alzheimers. The Functional protein sequences in FASTA for these genes are collected from NCBI (National center for Biotechnology information, http//www.ncbi.nih.nlm.gov/). These sequences are given to ClustalW (ref: http// www.ebi.ac.uk/ClustalW/) for the Multiple sequences Alignment (It calculates the best match for the selected sequences and lines them up so that identities , similarities and differences can be seen).

3. DISCUSSION

The genes which are hypothesised to be involved in causing Glaucoma and Alzheimers are retrieved from Genecards(genecards.org). The appropriate FASTA sequences are collected from NCBI. The genes with

maximum tissue type brain and eye are been selected for multiple Sequence alignment.

TABLE 1. Table showing the genes/proteins that have been involved in the present study, which are believed to cause Glaucoma and Alzheimers.

SNO	GENE SYMBOL	PROTEIN ID	LENGTH aa	TISSUE TYPE	Gc ID
1.	ADORA1	AAH26340	326aa	Brain, hypothalamus	GI:20070961
2.	ADRB2	AAA88017	413aa	Epidermis	GI:178204
3.	AGER	AAX07272	404aa	Lung	GI:59799494
4.	APOE	AAH03557	317aa	Eye, retinoblastoma	GI:13097699
5.	AQP1	AAL87136	265aa	Articular cartilage	GI:19387211
6.	AQP4	AAH22286	323aa	Lung	GI:18490380
7.	CASP12	Q6UXS9	341aa	No tissue type	GI:74749429
8.	CFLAR	AAH01602	480aa	Lymph, Burkitt lymphoma	GI:12804401
9.	CLU	AAH10514	449aa	Brain, glioblastoma with EGFR amplification	GI:14714741
10.	CNR1	AAI00969	472aa	PCR rescued clones	GI:71682703
11.	CNTF	AAH68030	200aa	White Matter pool-5 brain tissues-femoral artery, olfactory tract, optitract, cerebellar white matter, cerebral white matter."	GI:45751571
12.	CRYAB	AAH07008	175aa	Heart	GI:13937813
13.	FLOT1	AAI28155	237aa	PCR rescued clones	GI:124504560
14.	GAPDH	AAH83511	335aa	Lung, small cell carcinoma	GI:53734502
15.	GJA1	AAH26329	382aa	Brain, hypothalamus	GI:20072866
16.	GSTM1	AAH24005	181aa	Testis	GI:18645139
17.	GSTT1	CAI30332	66aa	Lung	GI:66862636
18.	IL1A	AAH13142	271aa	Lung, large cell carcinoma	GI:15341913
19.	NOS2A	AAI30284	1153aa	Pooled, cerebellum, kidney, placenta, testis, lung, colon, liver, heart, thyroid, bladder, uterus, PCR rescued clones	GI:120660146
20.	NOS3	AAI01211	192aa	PCR rescued clones	GI:133778229
21.	NPY	AAA59944	97aa	Pheochromocytoma	GI:189274
22.	PON1	AAH74719	355aa	Brain, PCR rescued clones	GI:50959528
23.	SNCB	AAH02902	134aa	Lung, small cell carcinoma	GI:12804099
24.	SNCG	AAH14098	127aa	Colon, adenocarcinoma	GI:15559465
25.	TTR	AAH05310	147aa	Liver	GI:13529050
26.	TYR	AAH27179	377aa	Skin, melanotic melanoma	GI:20072606

Based on the results from ClustalW, the scores Table and Phylogram Tree are derived. The Phylogram tree shows the distance between the protein sequences .

PHYLOGRAM

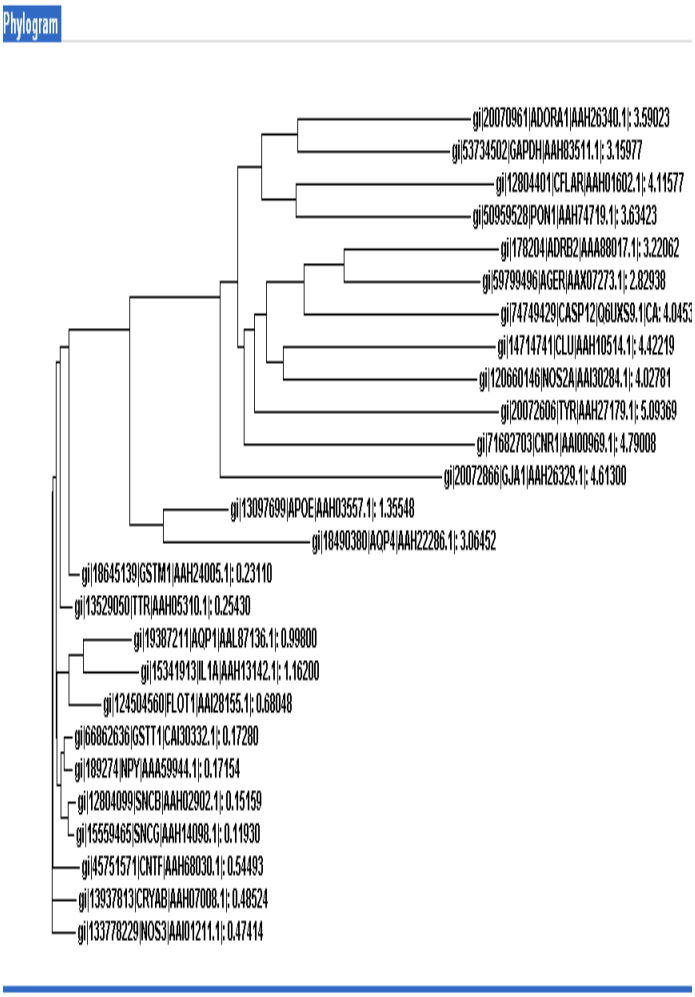

TABLE 2: Gene symbols with Phylogram distances.

S.NO	GENE SYMBOL	PROTEIN ID	DISTANCE
1	ADORA1	AAH26340	3.59023
2	ADRB2	AAA88017	3.22062
3	AGER	AAX07272	2.82938
4	APOE	AAH03557	1.35548
5	AQP1	AAL87136	0.99800
6	AQP4	AAH22286	3.06452
7	CASP12	Q6UXS9	4.04533
8	CFLAR	AAH01602	4.11577
9	CLU	AAH10514	4.42219
10	CNR1	AAI00969	4.79008
11	CNTF	AAH68030	0.54493
12	CRYAB	AAH07008	0.48524
13	FLOT1	AAI28155	0.68048
14	GAPDH	AAH83511	3.15977
15	GJA1	AAH26329	4.61300
16	GSTM1	AAH24005	0.23110
17	GSTT1	CAI30332	0.17280
18	IL1A	AAH13142	1.16200
19	NOS2A	AAI30284	4.02781
20	NOS3	AAI01211	0.47414
21	NPY	AAA59944	0.17280
22	PON1	AAH74719	3.63423
23	SNCB	AAH02902	0.15159
24	SNCG	AAH14098	0.11930
25	TTR	AAH05310	0.25430
26	TYR	AAH27179	5.09369

The genes with minimum distances are Synuclein beta(SNCB – 0.15159) and Synuclein gamma(SNCG – 0.11930). Hence SNCB,SNCG are believed to be involved in causing Alzheimers and Glaucoma.

3.1: SYNUCLEINS IN ALZHEIMERS AND GLAUCOMA

Synucleins are small proteins associated with neurodegenerative diseases .In glaucomatous individuals, nerve bundles are immuno positive for gamma synuclein; however, a strong gamma synuclein immuno positive staining in a subset of glial cells was observed in the lamina and postlamina cribrosa regions of the optic nerve in glaucoma patients. In the optic nerve of rats with episcleral vein cauterization used as an animal model of glaucoma, the quantity of both gamma synuclein mRNA and protein was decreased compared with the optic [4].

Synuclein proteins are produced, in vertebrates, by

three genes. They share structural resemblance to apolipo proteins, but are abundant in the neuronal cytosol and present in enriched amounts at presynaptic terminals. Synucleins have been specifically implicated in disease: Alzheimer's(AD). In AD, a peptide derived from alpha synuclein forms an intrinsic component of plaque amyloid.[5].

4. CONCLUSION

It is evident from the present study and results of previous investigations that Glaucoma and Alzheimers is a complex process in which Synucleins,GSTT1,NPY play a significant role .

In Alzheimer's disease patients, immuno histochemical staining for gamma-synuclein revealed the loss of immuno reactivity in the nerve fiber layer and the appearance of immunopositive cells in or near the outer nuclear layer. We conclude that, in mature eyes, synucleins are present predominantly in the retina and optic nerve, and the immuno reactivity of gamma-synuclein changes specifically in the retina of Alzheimer's disease patients too.

Immuno histochemical examination of 20 brains, using antibodies to alpha, beta, and gamma synuclein, demonstrated many alpha synuclein positive Lewy bodies and dystrophic neurites in 50% of brains with Alzheimer's disease. Similar lesions were less common in other regions of these brains, none of which contained beta-synuclein or gamma-synuclein abnormalities. Thus, alpha synuclein positive Lewy bodies and neuritic processes frequently occur with Alzheimer's disease in Down's syndrome brains [6][7][8].

More knowledge about the role of genes causing these diseases could lead to better diagnostic tools that will find glaucoma in its earliest stages before nerve damage begins which could be useful in diagnosing alzheimers also. This bioinformatics approach of finding genes causing diseases would help in developing Drugs that clear the bad amyloid protein which could prove to be useful in treating both these diseases.

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