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To build and analyze the network of pathways associated with Alzheimer's disease in Drosophila melanogaster and C.elegans

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ABSTRACT

Alzheimer's disease is progressive disease that destroys memory and other important mental function. In this project I studied the pathways associated with Alzheimer's disease in Drosophilamelanogaster and C.elegans which shows the common set of proteins and genes derived from wnt signalling pathway and protein processing in ER present in Alzheimer's and further I am done with Networks of proteins and genes using databases like EsyN and STRING. According to networks of genes and proteins I found, pathway of Homo sapiens is dependent pathway because the common protein GAPDH has been interacting with neurodegenerative disease-associated proteins, including the APP, BACE1, APOE, PSEN1 and ADAM10 which can lead to Alzheimer's disease. Hence if GAPDH will be considered as a target protein and its potential inhibitors could be found , it will lead to inhibit or cure the neurodegenerative diseases .

Keywords: KEGG, STRING Database, Alzheimer's disease, Networks .

I. INTRODUCTION

Alzheimer's disease (AD) also referred to simply as Alzheimer's is a chronic neurodegenerative disease that usually starts slowly and worsens over time. It is the cause of 60% to 70% of cases of dementia. The most common early symptom is difficulty in remembering recent events (short-term memory loss). As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self care and behavioural issues. As a person's condition declines, they often withdraw from family and society. The cause of Alzheimer's disease is poorly understood. About 70% of the risk is believed to be genetic with many genes usually involved. Other risk factors include a history of head injuries, depression or hypertension.

Dementia can affect a person in different ways, and progression of the disease depends upon the impact of the disease itself and the person's personality and state of health. Dementia can be divided in three stages:

- ✓ early stage: first year or two year.
- ✓ middle stage: second to fourth or fifth years.
- ✓ late stage: fifth year and after.

II. PROGRAMS

KEGG PATHWAY DATABASE:

KEGG is a database resource for understanding high-level functions and utilities of the biological system such as the cell, the organism and the ecosystem from genomic and molecular-level information. It is a computer representation of the biological system, consisting of molecular building blocks of genes and

proteins and chemical substances (chemical information) that are integrated with the knowledge on molecular wiring diagrams of interaction, reaction and relation networks . It also contains disease and drug information as perturbations to the biological system. EsyN Database - esyN(Easy Networks) is an open source bioinformatics web-tool for visualizing, building and analysing molecular interaction networks. esyN is based on cytoscape.js and its aim is to make it easy for everybody to perform network analysis. esyN is connected with a number of databases - specifically: pombase, flybase and most InterMine data warehouses, DrugBank and BioGRID from which its possible to download the protein protein or genetic interactions for any protein or gene in a number of different organisms.

Following pathways derived using KEGG Database.

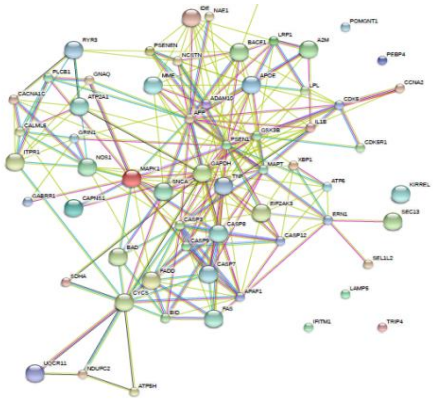

Figure 1

2.2 Amyloid Plaque Formation in Alzheimer's DiseaseSignaling Pathway -

Alzheimer's disease is one of the most common neurodegenerative diseases worldwide. Clinically, it is characterized by the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles, resulting in neuronal dysfunction and cell death. Central to this disease is the di ecential processing of the integral membrane protein APP (Amyloid Precursor Protein) in the normal versus disease state. In the normal state, APP is initially cleaved by α-secretase to generate sAPP and a C83 carboxy-terminal fragment.

1) Mild Alzheimer's

The first stage usually lasts from 2 to 4 years.

The symptoms include:

- Having less energy and drive to do things
- Less interest in work and social activities and spending more time just sitting, watching TV or sleeping
- Loss of recent memories like forgetting conversations and events that just happened
- Language problems like trouble putting their thoughts into words or understanding others
- Mild coordination problems such as trouble writing or using familiar objects.
- A hard time with everyday tasks such as following a recipe or balancing a checkbook
- Mood swings that involve depression or a lack of interest

2) Moderate Alzheimer's

This is when memory loss gets worse and starts to cause problems in daily life. This stage can last from 2 to 10 years. Someone with moderate Alzheimer's may start to forget details about his life, like where he went to high school or when he got married. He may not recognize or remember family members and friends. He might also forget where he leaves things and can't retrace his steps to find them.

Other symptoms at this stage can include:

Trouble coming up with the right words and using the wrong ones

- A hard time planning or solving problems
- Confusion about time or place. He may get lost in places he's been before. Once he's there, he may not know how or –why he got to that place.
- Getting angry or upset easily, sometimes lashing out at family or caregivers
- Trouble sleeping
- Wandering

Some people with moderate Alzheimer's also become more aware that they're losing control of their lives,

which can make them even more frustrated or depressed.

3) Severe Alzheimer's

The third stage also known as late Alzheimer's, is the most severe. It typically lasts 1 to 3 years.

People in this phase might have some or all of these symptoms:

Major confusion about what's in the past and what's happening now

- Can't express themselves, remember or process information
- Problems with swallowing and control of their bladder and bowels
- Weight loss, seizures, skin infections and other illnesses
- Extreme mood swings
- Seeing, hearing or feeling things that aren't really there, called hallucinations

Alzheimer Disease in homo sapiens					
Alzheimer Disease in *homo*		Protein processing in endoplasmi		WNT Signalling Pathway	
Sr. no	Protein Names	Sr. no	Protein Names	sr.no	Protein Names
1	APP (Amyloid Precursor Protei	1	Translocon (protein export)	1	cononical pathways
	APP-BP1		Sec61		Porc
	Fe65		Sec62/63		Cer-1
	GAPD	2	Ribosome anchor		Netun
	BACE (β-Secretase)		OSTs		FRP
	RTN3/4		Glcll		WNT
	PEN2,PSEN		Climp63		Wif-1
	NCSTN,APH-1	3	protein recognition by luminal chaperones		SOST
2	Amyloide β (Aβ)		NEF		Dkk
	LPL,ApoE		BiP		BAMBI
	LRP——>Aβ aggregation		GRP94		LRP5/6
3	oligomeric intracellular Aβ		Hsp40		CKI
	Cx IV	4	Ribosome		GSK-3
	ABAD		SRP		ICAT
4	Oligomeric Aβ		SR		TCF/LEF
	GPCR		SRP		CtBP
	Gq	5	Translocon		CBP
	PLC		BiP		c-myc
	NMDAR		G3M9		c-jun
	VDCC	6	COPII		fra-1
5	Fragmentation		SAR1		cycD
	SNCA		Sec13/31		PPAR
	NAC		Sec23/24		Uterine
6	Microglia		Sec12	2	planar cell polarity(PCP)
	TNF	7	ER-associated degradation(ERAD)		Wnt11
	IL-1		Hsp70		knypek
7	Mitochondria		Hsp40		Frizzled
	Cx I		NEF		Stbm
	Cx II		Hsp90		INVS
	Cx III		DSK2		Dvl
	Cx IV		RAD23		Daam1
	Cx V		sHSF		RhoA
	ABAD(ATP depletion fall in mitoch		Otul		ROCK2
	CaM		p50 ATF6		JNK
	Cn		SVIP		Rac
			Fng1	3	Wnt/Ca2+ pathways

Figure 2

III. STRING DATABASE

In molecular biology, STRING (*Search Tool for the Retrieval of Interacting Genes/Proteins*) is a biological database and web resource of known and predicted protein–protein interactions.

The STRING database contains information from numerous sources, including experimental data, computational prediction methods and public text collections. It is freely accessible and it is regularly updated. The resource also serves to highlight functional enrichments in user-provided lists of proteins using a number of functional classification systems such as GO, Pfam and KEGG.

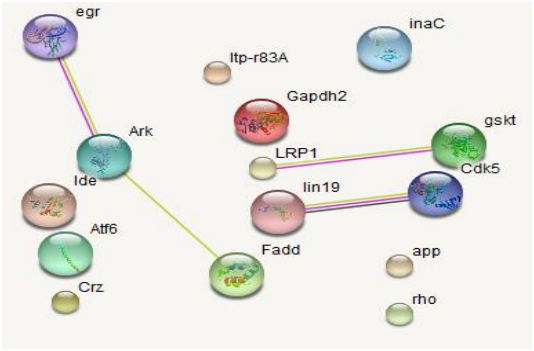

Figure 3

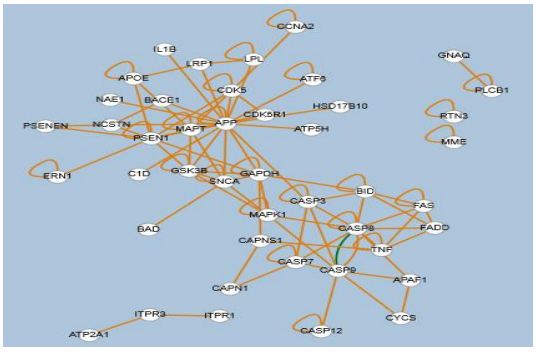

Figure 4

IV. PROTEIN-PROTEIN INTERACTIONS

Protein interactions are fundamentally characterized as stable or transient and both types of interactions can be either strong or weak. Stable interactions are those associated with proteins that are purified as multi-subunit complexes and the subunits of these complexes can be identical or different. Hemoglobin and core RNA polymerase are examples of multi-subunit interactions that form stable complexes. Transient interactions are expected to control the majority of cellular processes. As the name implies, transient interactions are temporary in nature and typically require a set of conditions that promote the interaction, such as phosphorylation, conformational changes or localization to discrete areas of the cell.

Alzheimer's disease (AD) is the most common form of dementia. It is the sixth leading cause of death in old age people. Despite recent advances in the field of drug design, the medical treatment for the disease is purely symptomatic and hardly effective. Thus there is a need to understand the molecular mechanism behind the disease in order to improve the drug aspects of the disease.

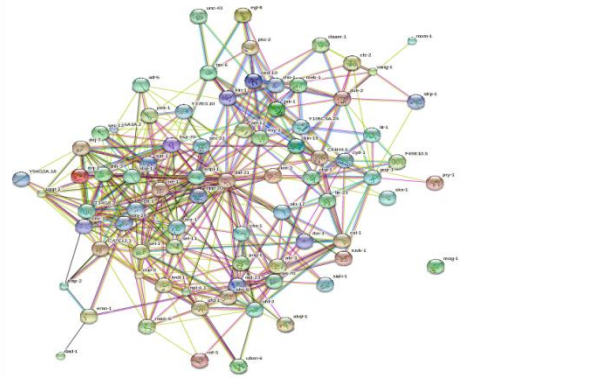

Figure 5

V. RESULT AND CONCLUSION

We tried to find the network of three pathways associated with Alzheimer's diasese in *Homo sapiens*, *Drosophila melanogaster* and *C.elegans* obtained from databases like KEGG, EsyN and STRING. Results are showing in the above figers, The protein GAPDH is common protein in the pathways of *Homo sapiens* and *Dro*sophila melanogaster but not in *C.elegans*.

The pathway of *Homosapiens* is dependent pathway because the common protein GAPDH has been interacting with neurodegenerative disease-associated proteins, including the APP, BACE1, APOE, PSEN1 and ADAM10 which can lead to Alzheimer's disease.

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