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Effect of Dopamine on Alzheimer and Autism and Determination of Best Model Organism for Both

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Abstract- As medicinal science heading towards the new discoveries, butthe trap of psychological disorders, kept questioning about the capabilities of medicinal science. They sinisterly kill people through their slow poisons like dementia, depression as well as in form different diseases like Schizophrenia, Alzheimer, Autism, Parkinson and many others. In our study we focused on analysis of two totally different diseases that are Alzheimer and Autism. Former one affect the old stage while later shows its presence in childhood stage of us Homo sapiens life. Many neurotransmitters, proteins and various chemicals play their different roles in these two disorders. But certainly Dopamine which is a monoamine synthesized from amino acid tyrosine is a common neurotransmitter play its vital role by varying its percentage in these two diseases. Due to dopamine's soluble nature, in case of Alzheimer aggregates with beta-peptide while in Autism's case it affect the central nervous system (CNS). In between huge number of genes of Dopamine, we selected the Dopamine beta hydroxylase gene, which help in combining the study of Alzheimer and Autism together, using different Bioinformatics tools, and proteomic and gene expression analysis. On such basis, among Bos tarus, Rattus norvegicus, Mus musculus, Canis lupus, Danio rerio, Homo sapiens and Equus caballus, we determined the best model organism for Alzheimer and Autism and which may help in future aspects of pharmacogenomics & personalized medicines for both.

Index Terms- Alzheimer, Autism, Dopamine, Dopamine beta hydroxylase, PEPSTATE, Arrayexpress.

I. INTRODUCTION

Brain, the fundamental unit of every mammalian isclaimed to be the motherboard of Homo sapiens body system. But as science moving violently so fast via us, we are being conquered by different psychological problems like Schizophrenia, Autism, Dyslexia, Alzheimer etc. In our study we are interested in Alzheimer and Autism. These two diseases are poles apart from each otherbut have disastrous results in common like social impairment etc.

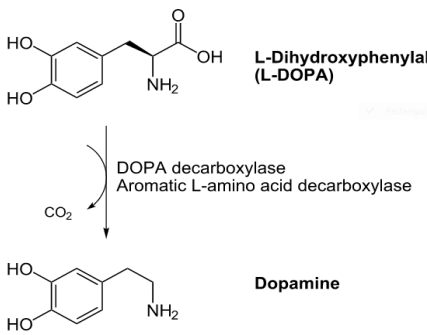
Alzheimer as a degenerative age related disease, impairs an individual's cognitive abilities; started with impaired memory and followed by impaired thoughts, speech and ended with complete helplessness. In result of Alzheimer, there is extreme shrinkage in cerebral cortex and hippocampus with severely enlarged ventricles as stated by different researchers and various brain analyses(*Arch Neurol*. 2007)

"As per CDC (center for disease control) report, study says about 5 million Americans in which 13% are of 65 years while the rest 50% are either of 85 years or above. It is concluded that number of patients may increase to 16 million as 70% of patients live at home and its impact may extendsto millions of family members, friends and caretakers" (*kukull et al. 2002 & R. tarawneh and D. M. Holtzman 2012)*

Autism is a psychic condition, started from early childhood is characterized by absorption in self-centered subjective mental activity, especially when accompanied by marked withdrawal from reality, inability to interact socially, repetitive behavior and language dysfunction.

"For Autism CDC report for united state, the autism rate skyrocket to 1 in 88 children in 2008, a 78% increase over 2002 that is about 1 in 156."Amygadala in brain, responsible for emotional responses, including hyperactivity, stereotype and negativism and is also found undeveloped in an autistic child. According to our goggling knowledge and studies an autistic child has 50mm larger brain than an average normal child.

Dopamine which is a neurotransmitter belongs to transferase of EC2 class having molecular name i.e. Dopamine N acetyl transferase isoform A (via RASMOL). It is characterized due to its soluble nature and is biosynthesized in the neuron tissue and medulla of the adrenal gland of our body. First by the hydration of amino acid L- tyrosine to L- Dopa via the enzyme tyrosine-3-monooxygenase, also known as Tyrosine hydroxygenase and then by the decarboxylation of L-Dopa by aromatic L-amino acid decarboxylase.



Dopamine along with human and other animals plays different key functions that are in, movement, memory, pleasurable reward, behavior and cognition, attention, inhibition of prolactin production, sleep, mood, and learning.

But certainly in case of Alzheimer, dopamine aggregates with Beta- Amyloid peptide. Patients of Alzheimer have an abundance of Plaques & Tangles wher plaques are

deposits of protein fragment Beta- amyloid and tangles are twisted fibers of another protein called as Tau. (*Nat Rev Neurol*. 2010). While in case of Autism, dopamine's gene DBH (Dopamine-beta hydroxylase), convert dopamine into norepinepherine expressed in neuron and in neuroendocrine cell and therefore DBH could also be a modifier of Autism risk (Autism Res. 2011)

II. METHADOLOGY

For obtaining the satisfying results, we performed various bioinformatics' tools and technique. In this queue of procedure we searched for 'NCBI' (National center for biotechnological information), which is a part of the United States national library of medicines (NLM), a branch of the National institute of Health. NCBI houses genome sequencing data in GenBank and an index of biomedical research articles in Pubmed central and Pubmed, as well as other information relevant to biotechnology. All these databases can be searched online through the Entrez searched engine. (Reference to 'GenBank: the nucleotide sequence database, Chapter 1).
By using NCBI's research articles we studied about Alzheimer and Autism as well as dopamine's role both the cases and its genes.

In our second step, we selected Bioinformatics' tool that is 'Uniprot KB', which comprises the EBI (European bioinformatics institute), SIB (Swiss institute of Bioinformatics) and PIR (Protein information resources). It consists of high quality and freely accessible database of protein sequences. (Reference to Uniprot.C. 2010: "ongoing and future developments at the universal protein resources).
As per 'Uniprot KB' results about dopamine, it concluded, dopamine comprises different types of genes that are DRD4, DBH, DRD3, DOP – 3T14E83, DRD5, SLC6A3, SLC6A2, SLC6A4, DDC, CDNF.ARMELT 1, DOPR2 DAMB DOP R99B CG18741, etc shows there presence in various organism like, Homo sapiens (Human), Didelphis virgeniana (North American opossum), Carassius auratus (Gold Fish), Canis lupus (Grey wolf), Danio rerio (Zebra fish), Equuas caballus (Plain region Horse), Mus musculas (House mouse), Bos tarus (Cow), Rattus novegicus (Brown rat), Pan troglodytes (Chimpanzee), etc.
But we found, DBH gene as most common in different organisms with varying length. On this basis, we selected seven model organisms for determination of result that are, Canis lupus (Grey wolf), Danio rerio (Zebra fish), Equuas caballus (Plain region Horse), Mus musculas (House mouse), Bos tarus (Cow), Rattus novegicus (Brown rat), Homo sapiens (Human). So we selected DBH gene of seven model organism for performing various experiments related to Autism and Alzheimer.
After selecting the model organism, we move towards to find out the 'FASTA sequence' of dopamine gene in above selected organism. By using these nucleotide sequences, we undergo proteomic analysis via two different methods.
First,by uses a tool of EBI 'Transeq'. Transeq reads one or more nucleotide sequence from FASTA and writes the corresponding protein sequence translation of dopamine's gene DBH of selected organisms to file.
Further, EMBOSS's (European molecular biology open software suite) tool PEPSTAT, which reads one or more protein sequences that we have and write an output file with various statics on protein properties, which includes weight no. of residue charges, iso-electric point, molar extinction coefficient for each type of amino acid, number & molar percentage, etc. and this results in identifying the amino acids in loaded proportion. By using these amino acids we can work on model organisms and can be used for curing Alzheimer and Autism.

After obtaining the amino acids, we worked on 'CPG report' which identifies the CPG islands in one or more nucleotide sequences. Our next mission was to find out the number of DBH genes over and under expressed in the organs of the model organism. For this we perform gene expression analysis for DBH gene, using 'ARRAY EXPRESS tool', which is a database of functional genomics experiments including gene expression where you can query and download data collected to MIAME and MINSEQE stands.

In the end we plot a phylogenetic tree between the model organisms using phylogenetic analysis via clustal w2, which is a command line interface that offers a significant increase in scalability allowing hundreds of thousands of sequences to be aligned in only a few hours. By plotting this phylogenetic tree, we can relate all model organisms to each other and can get to know about the best model organism to study for Alzheimer and Autism.

III. RESULTS

By using PEPSTAT, we find out, Proline and Leucine amino acid in loaded percentage, along with Serine in the selected model organism.

Amino acids presents in model organisms are listed below:

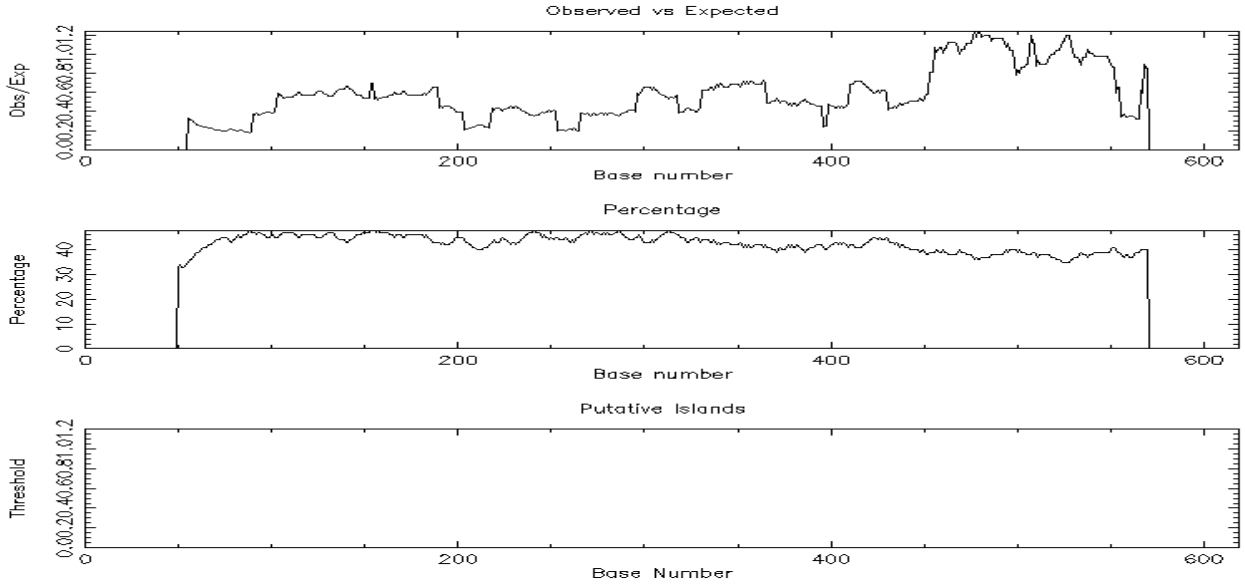
- Bos tarus – Proline
- Rattus norvegicus – Leucine
- Mus musculus – Serine
- Canis lupus – Proline
- Equus caballus – Proline
- Danio rerio – Leucine
- Homo sapiens – Leucine

When we obtain the amino acids, we worked for CPG report, which shows:

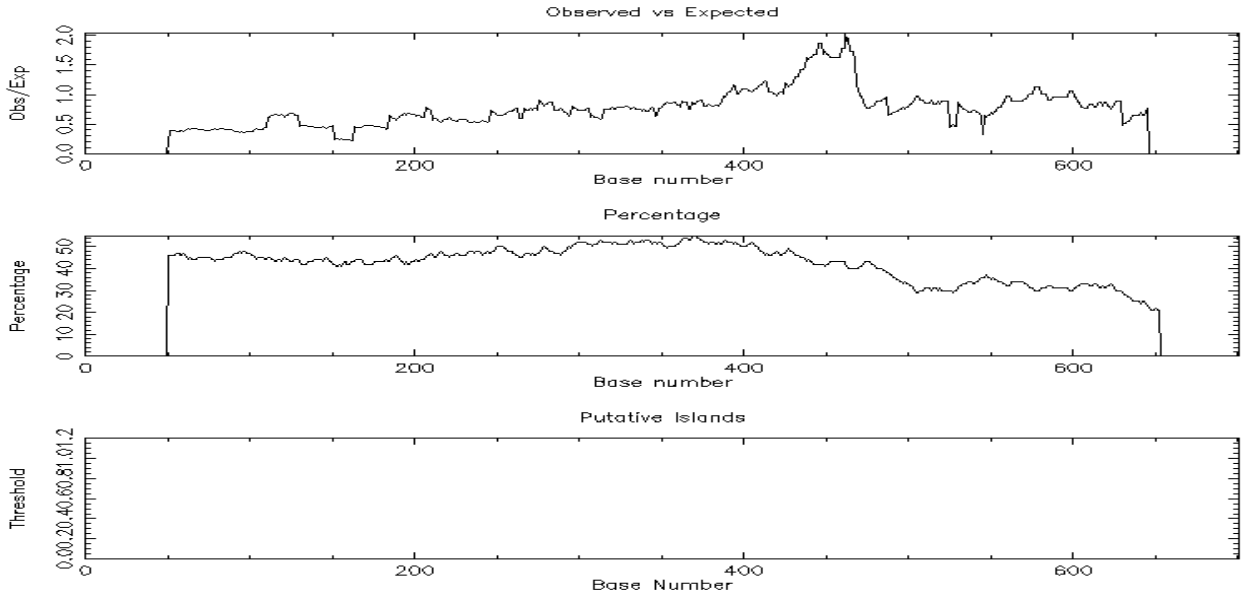
For Leucine:

CPG plot island of unusual composition.

CV012661from 1to 620
Observed/expected ratio > 0.60
Percent cytosine + percent guanine > 50.00
Length > 200
The given figure explains the CPG plot for leucin:



For Proline:
CPG plot island of unusual CG composition
FK811785 from 1 to 702
Observed/expected ratio > 0.60
Percent cytosine + percent guanine > 50.00
Length > 200
The given figure explains the CPG plot for Proline

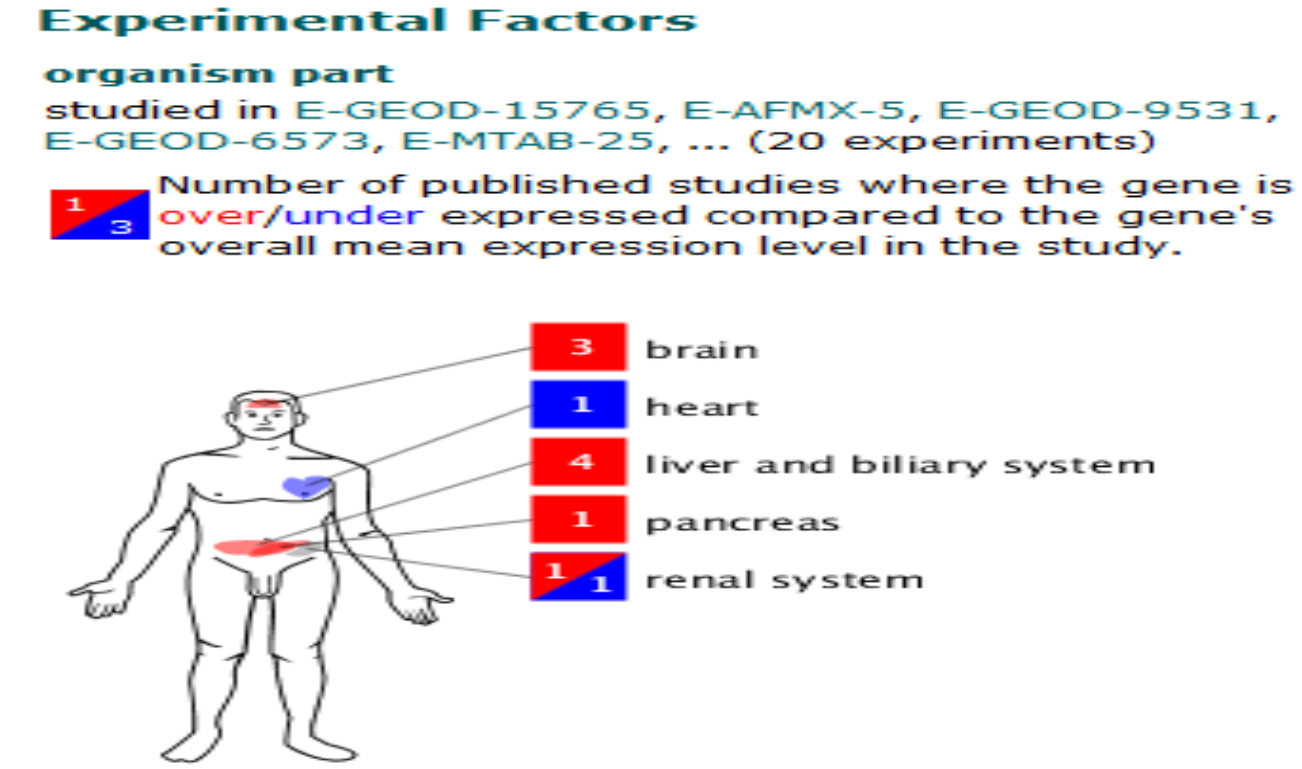


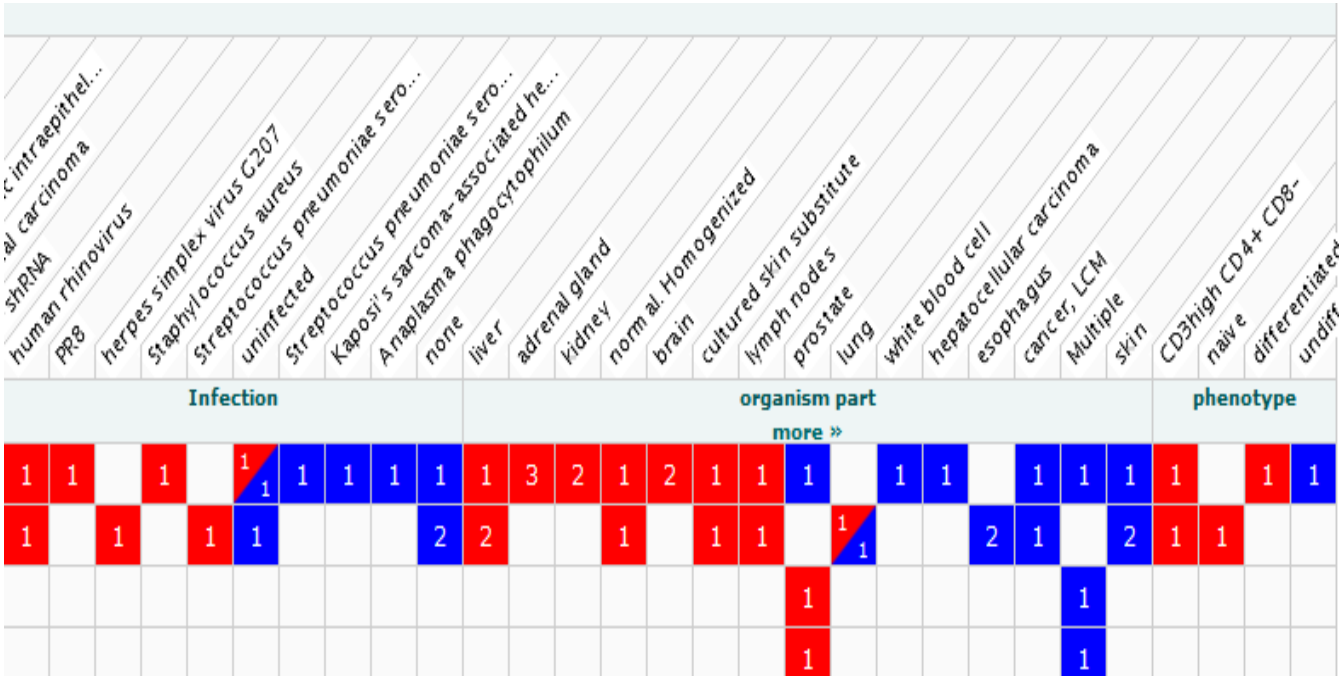
On using ARRAY EXPRESS tool for gene expression analysis, to find over/ under expressed gene DBH with respect to Homo sapiens, we got that in following given organs, the given number of DBH genes are over/under expressed:

Brain – 3 genes
Heart – 1 gene
Liver & Biliary system – 4 genes
Pancreas – 1 gene

Renal system – 2 genes

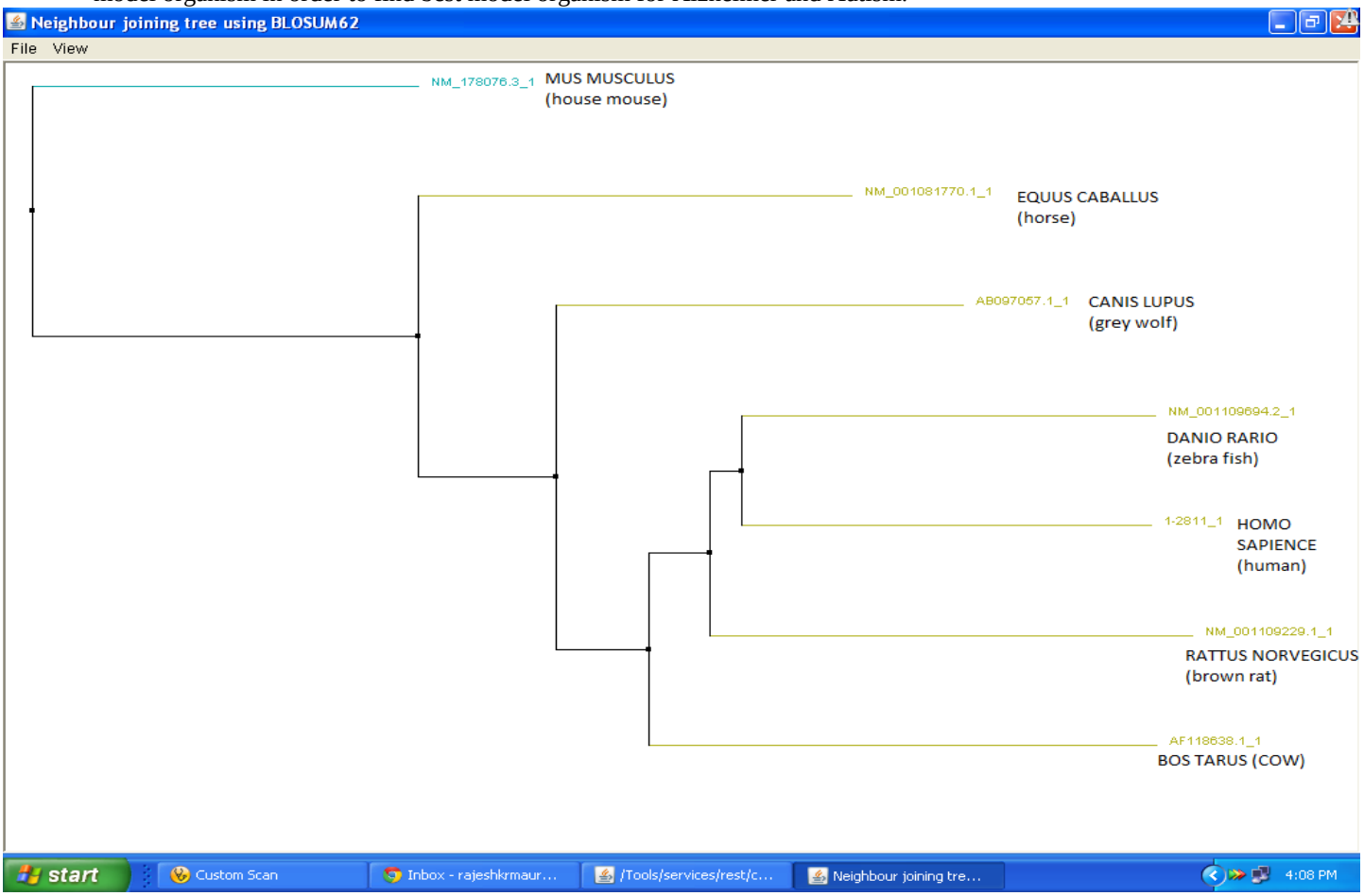
The over and under expressed genes in body of Homo sapiens are explained in figures given, obtained from analysis via the given tool.





***NOTE:Blue color* indicates toward under expressed while red color supports for over expressed DBH gene in Homo sapiens.**

A phylogenetic tree is obtained as a result of phylogenetic analysis using BLOSUM62 via clustal w2 which correlate the model organism in order to find best model organism for Alzheimer and Autism.



IV. CONCLUSION

1.According to our theoretical aspects, Dopamine which belongs to catecholamine family is a neurotransmitter and is a chemical messenger that helps in the transmission of signals in the brain and other vital areas (Reference to article reviewed by April cashin – Garbutt, BA hons (cantals)); synthesized in nervous tissue and the medulla of the adrenal gland in our body, define its roles in behavior and cognition, motor activity, motivation, reward, regulation of milk production, sleep, mood, attention, and learning (Reference live strong article no : 425629) . Since Alzheimer and Autism both revolve around the individuals' social, behavioral, and cognition problems. Dopamine is the only neurotransmitter which is common in case that affect both the diseases with its varying amount. Hence after the various experiments and articles though, we focused on dopamine's gene DOPAMINE BETA HYDROXYLASE (DBH), which is a protein and using this gene we can work on AUTISM as well as on ALZHEIMER.

2. According to our dry laboratory aspects, though dopamine is synthesized from amino acid tyrosin (Reference to various dopamine related journals onNCBI, EBI and many others), but when we use DBH of model organisms 'selected' for derivation of amino acids responsible in both diseases as a result of PEPSTAT tool, we found Leucine and Proline are the amino acids present as eye-catching loaded amount in maximum model organism. Serine also showed it high percentage in Mus musculus. As per CPG report, the no. of CG Rich Island is zero for leucine and proline. The phylogenetic analysis says Rattus norvegicus, Danio rerio and Homo sapiens are closely linked. Hence we end up with leucine amino acid as amino acid selected; since it is the only amino acid in higher percentagein the co- related model organism used for Autism and Alzheimer.

3. Due to ethnic and social issues we can't work on Homo sapiens. Though we can consider Danio rerio as best model organism for both the diseases but due its condition of less and not easily availability in laboratories and complicated in analysis, we have chosen **Rattus norvegicus as best model organism for analyzing the cases of Autism and Alzheimer.**

4. By using Rattus norvegicus as best model organism, we can turn up in field of personalized medicines and pharmacogenomics as future aspects for Alzheimer and Autism cases.

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