

**DATA ANALYTICS OF NEURODEVELOPMENTAL DISORDERS USING
COMPUTATIONAL APPROACHES.**

Submitted in partial fulfillment of the requirements for the award of
Bachelor of Engineering Degree in
BIOINFORMATICS

By

**ANNA ROCK (Register No. 3622004)
CHIRUMAMILLA KRISHNA PRASAD (Register No. 3622018)**



DEPARTMENT OF BIOINFORMATICS

SATHYABAMA

**INSTITUTE OF SCIENCE AND TECHNOLOGY
(DEEMED TO BE UNIVERSITY)**

Accredited with Grade "A" by NAAC

JEPPIAAR NAGAR, RAJIV GANDHI SALAI, CHENNAI - 600 119

APRIL 2020



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DEPARTMENT OF BIOINFORMATICS BONAFIDE CERTIFICATE

This is to certify that this Project Report is the bonafide work of
ANNA ROCK(Reg. No. 3622004) and **CHIRUMAMILLA KRISHNA PRASAD** (Reg. No. 3622018)
who carried out the project entitled "**DATA ANALYTICS OF NEURODEVELOPMENTAL
DISORDERS USING COMPUTATIONAL APPROACHES**" under our supervision from December
2019 to April 2020.

Dr. DANIEL ALEX ANAND
Internal Guide

Dr. JEMMY CHRISTY
Head of the Department

Submitted for Viva voce Examination held on_____

Name:

Signature:

Internal Examiner

External Examiner

DECLARATION

We **ANNA ROCK** (Reg. No. 3622004) and **CHIRUMAMILLA KRISHNA PRASAD** (Reg. No. 3622018) hereby declare that the Project Report entitled **“DATA ANALYTICS OF NEURODEVELOPMENTAL DISORDERS USING COMPUTATIONAL APPROACHES”** done by us under the guidance of **Dr. DANIEL ALEX ANAND** is submitted in partial fulfillment of the requirements for the award of Bachelor of Engineering degree in BioInformatics.

1.

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SIGNATURE OF THE CANDIDATES

ACKNOWLEDGEMENT

We are pleased to acknowledge our sincere thanks to Board of Management of **SATHYABAMA UNIVERSITY** for their kind encouragement in doing this project and for completing it successfully. We are grateful to them.

We convey our thanks to **Dr. JEMMY CHRISTY, Head of the Department, Dept. of BioInformatics** for providing us necessary support and details at the right time during the progressive reviews.

We would like to express our sincere and deep sense of gratitude to our Project Guide **Dr. DANIEL ALEX ANAND** for his valuable guidance, suggestions and constant encouragement paved way for the successful completion of our project work.

We wish to express our thanks to all Teaching and Non-teaching staff members of the Department of BioInformatics who were helpful in many ways for the completion of the project.

INDEX

CHAPTER No.	TITLE	PAGE No.
	ABSTRACT	V
1.	INTRODUCTION.	
	1.1. NEURODEVELOPMENTAL DISORDER.	1
	1.2. REVIEW OF LITERATURE.	2
2.	LITERATURE SURVEY.	
	2.1. BOOKS THAT DOCUMENTED SAVANT SYNDROME.	9
	2.2. ARTICLES RELATED TO SAVANT SYNDROME.	12
3.	AIM & SCOPE.	
	3.1. AIM	20
	3.2. SCOPE OF THE PROJECT.	
4.	EXPERIMENTAL USE.	
	4.1. ARCHITECTURE DIAGRAM. 4.2. SYSTEM REQUIREMENT. 4.3. HARDWARE REQUIREMENT. 4.4. SOFTWARE REQUIREMENT.	22
5.	RESULTS AND DISCUSSION.	
	5.1. MODULE-1.	24
	5.2. PATHWAY ANALYSIS.	32
6.	CONCLUSION.	49

ABSTRACT

The practice of data science requires the use of analytics tools, technologies and programming languages to help data professionals extract insights and value from data. A recent survey of nearly 24,000 data professionals revealed that Python, SQL and R are the most popular programming languages used for the biological approaches for analyzing huge biological data such as NeuroDevelopmental disorder such as Savant syndrome and Autism Spectrum disorder in particular which may be genetic or caused by any external physical injury. Savant syndrome is a condition in which someone with significant mental disabilities demonstrates certain abilities far in excess of average. These skills at which savants excel are generally related to memory. Approximately one in 10 persons with Autism Spectrum disorder has some savant skills. In other forms of development disability, mental retardation or brain injury, savant skills occur in less than 1% of such persons. Savant skills are usually found in one or more of five major areas: art, memory, arithmetic, musical abilities, and spatial skills. Advanced memory is the key "superpower" in savant abilities. It has been suggested that individuals with autism are biased towards detail-focused processing and that this cognitive style predisposes individuals either with or without autism to savant talents. So our desire is to estimatedly give the possibility of number of people out suffering neurodevelopmental disorder and to detect the main genetic cause and to analyze the data for further examination for networking of the homology using various biocomputational languages.

CHAPTER-1

INTRODUCTION

1.1.1 INTRODUCTION

NEURODEVELOPMENTAL DISORDER:

NeuroDevelopmental disorders are impairments of the growth and development of the brain and/or central nervous system. To be specific it refers to a disorder of brain function that affects emotion, learning ability, memory and self skill which unfolds as an effect as the individual develops and grows.

Causes:

Development of the nervous system is tightly regulated and timed; it is influenced by both genetic programs and the environment.

Any significant deviation from the normal developmental trajectory early in life can result in missing or abnormal neuronal architecture or connectivity.

AUTISM SPECTRUM DISORDER:

Autism Spectrum Disorder (ASD), is a range of mental disorders of the neurodevelopmental type. It includes autism and Savant syndrome. Individuals on the autistic spectrum often experience difficulties with social communication and interaction and may exhibit restricted, repetitive patterns of behavior, interests, or activities. Symptoms are typically recognized between one and two years of age. Long-term problems may include difficulties in performing daily tasks, creating and keeping relationships, and maintaining a job.



Fig 1.1(a)

Children Behavior with ASD.

SAVANT SYNDROME:

Savant syndrome is a condition in which someone with significant mental disabilities demonstrates certain abilities far in excess of average. The skills at which savants excel are generally related to memory. This may include rapid calculation, artistic ability, map making, or musical ability. Usually just one special skill is present.

Those with the condition generally have a neurodevelopmental disorder such as autism spectrum disorder or have a brain injury. About half of the cases are associated with autism and may be known as "autistic savants". While the condition usually becomes apparent in childhood, some cases may develop later in life. It is not recognized as a mental disorder within the DSM-5.

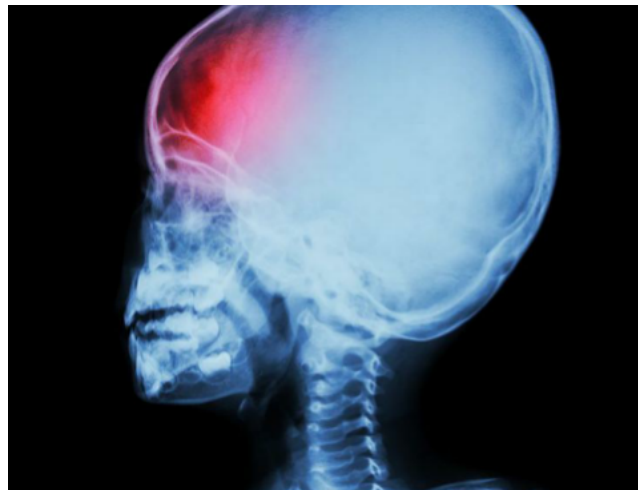


Fig 1.1(b)

Brain of a person with accidental Savant .

1.2 REVIEW OF LITERATURE

1.2.1 AUTISM SPECTRUM DISORDER

What is ASD?

Autism is a neurological developmental disability that hampers normal brain development, affecting communication, social interaction, cognition, and behavior.

Autism is known as a spectrum disorder because its symptoms and characteristics appear in a variety of combinations that affect children in different ways. Some children may have severe challenges and would need help while others may be able

to manage their tasks independently, with less help.

Earlier, each condition (autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), Asperger syndrome and Savant Syndrome) was diagnosed separately as disorders but now, these conditions are grouped together and are called as Autism Spectrum Disorder. But it is not recognized as a mental disorder within the DSM-5.

What are the signs of ASD?

The early signs of autism can be observed during the first three years of a child's life. These signs may vary from being mild, moderate, to severe. Also, the signs may vary from one child to another, and may change as the child grows. A child with severe cognitive impairment and motor skills may also develop epilepsy. However, a specific set of behaviors are indicators of the condition.

Conditions that co-exist with autism: Other conditions like mental retardation, hyperactivity, motor difficulties, seizures, learning disability, hearing or visual impairment may co-exist with autism and they may coexist with other syndromes such as "Savant syndrome".

What are the strengths and abilities of ASD?

Often in these cases the main focus is the weaknesses rather than the strengths of a person. A child with autism has certain abilities and aptitude, which parents, therapists, and teachers need to identify and encourage the child to make the most of his or her talents and skills.

The child may exhibit some of these skills:

- Good visual and spatial memory.
- Methodical and organized way of doing things.
- Ability to understand abstract concepts.
- Excellence in the area of their interest.
- Attention to detail.
- Interest in languages (among children who can speak well) (may develop in to an "orator").

Genetic reasoning for ASD:

ASD is a rare single nucleotide mutation. More recently, discoveries of rare point mutations and characterization of balanced chromosomal abnormalities have pinpointed individual ASD genes of relatively strong effect, including both loci with

strong a priori biological relevance and those that would have otherwise been unsuspected as high-priority biological targets. ASD is highly heterogeneous, with hundreds of genes capable of conferring varying degrees of risk, depending on their nature and the predisposing genetic alteration. Moreover, many genes that have been implicated in ASD also appear to be risk factors for related neurodevelopmental disorders, as well as for a spectrum of psychiatric phenotypes.

Treatment for ASD

The aim of the treatment is to target behaviors that will help the child improve their abilities to integrate into schools, develop meaningful relationships, and to increase the possibility of maintaining independent living as adults. Treatment interventions aim to increase socially acceptable and prosocial behavior, decrease odd behavior and improve verbal and non-verbal behavior.

Children with autism can make significant progress if the psychological intervention they receive is structured and consistent.

There are types of treatments for autistic children:

Applied Behavior Analysis (ABA):-

- Discrete Trial Training (DTT).
- Early Intensive Behavioral Intervention (EIBI).
- Pivotal Response Training (PRT).
- Verbal Behavior Intervention (VBI).
- Treatment and Education of Autistic and related Communication Handicapped Children Method (TEACCH).

1.2.2 SAVANT SYNDROME

Definition:

Savant syndrome occurs when a person with below normal intelligence displays a special talent or ability in a specific area.

What is Savant syndrome?

This syndrome is a condition in which someone with significant mental disabilities demonstrates certain abilities far in excess of average. The skills at which savants excel are generally related to memory. This may include rapid calculation, artistic ability, map making, or musical ability. Usually just one special skill is present.

Those with the condition generally have a neurodevelopmental disorder such as autism spectrum disorder or have a brain injury. About half of the cases are

associated with autism and may be known as "autistic savants". While the condition usually becomes apparent in childhood, some cases may develop later in life. It is not recognized as a mental disorder within the DSM-5. (DSM-5: The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition is the 2013 update to the Diagnostic and Statistical Manual of Mental Disorders, the taxonomic and diagnostic tool published by the American Psychiatric Association (APA). In the United States, the DSM serves as the principal authority for psychiatric diagnoses.) So after the release of the DSM-5 the diagnosis of the patients with savant was removed from the disorder to moved to syndrome.

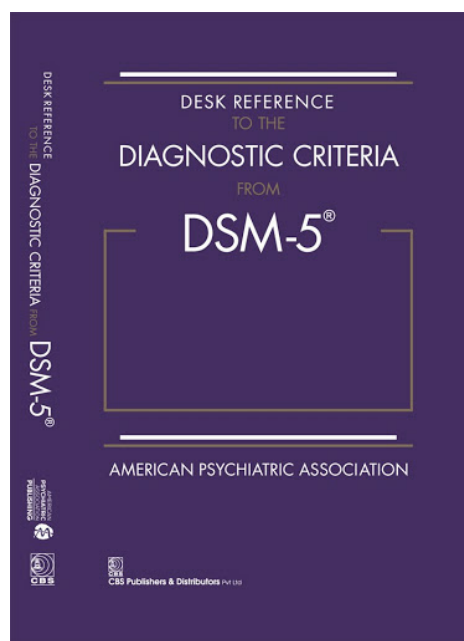


Fig 1.2.2(a)
This book is DSM-5.

Because a syndrome is different from a disease and disorder like in a:-

Disease: A particular distinctive process in the body with a specific cause and characteristic symptoms.

Disorder: Irregularity, disturbance, or interruption of normal functions.

Syndrome: A number of symptoms occurring together and characterizing a specific disease.

History of Savant syndrome:

Children who display savant syndrome have traditionally been referred to as idiot, retarded, or autistic savants. The negative connotations of the term "idiot" have led to the disuse of "idiot savant". Because the syndrome is often associated

with autism , the term autistic savant is more frequently heard. The first known description of a person displaying savant syndrome occurred in a German psychology journal publication titled "Gnothi Sauton" in 1751. The term savant was first used in 1887 by "J. Langdon Down"(the doctor for whom Down syndrome is named).

Demographics of Savant syndrome:

There were many reported cases of savant and many are related to ASD. About half of all children with savant syndrome are autistic. Approximately 10 percent of all children with autism have savant syndrome. The rate increases to 25 percent of children with autism who have an IQ over 35. (Many autistic children have lower IQs.) About three times as many boys as girls have savant syndrome. This may be because more boys than girls are affected with autism. Less than 1 percent of the non-autistic population, including those with mental retardation and other developmental disorders, have savant syndrome.

Causes and Symptoms of Savant syndrome:

Causes: of savant syndrome were as of 2004 not known. Some researchers hypothesize that it is caused by a change in a gene or genes, and others believe that it is caused by some kind of damage to the left hemisphere of the brain with compensation for this injury occurring in the right hemisphere. The reasons for the syndrome are not at all clear, however, and more research needs to be done.

Symptoms: There are no particular symptoms to identify the syndrome but children with savant syndrome have an exceptional talent or skill in a particular area, such as the ability to process mathematical calculations at a phenomenal speed. Savant skills occur in a number of different areas, including music, visual arts, and mathematics. Experts believe that the most common skill demonstrated by savants is "extraordinary memory". Children with savant syndrome may be able to memorize extensive amounts of data in such areas as sports statistics, population figures, and historical or biographical data. One particular skill common to those with savant syndrome is the "ability to calculate" what day of the week a particular date fell on or will fall on. So the people around these children should pay attention to these exceptions.

Mechanism of Savant syndrome:

Psychological:

No widely accepted cognitive theory explains savants' combination of talent and

deficit. It has been suggested that individuals with autism are biased towards detail-focused processing and that this cognitive style predisposes individuals either with or without autism to savant talents. Another hypothesis is that savants hyper-systemize, thereby giving an impression of talent. Hyper-systemizing is an extreme state in the empathizing–systemizing theory that classifies people based on their skills in empathizing with others versus systemizing facts about the external world. Also, the attention to detail of savants is a consequence of enhanced perception or sensory hypersensitivity in these unique individuals. It has also been confirmed that some savants operate by directly accessing low-level, less-processed information that exists in all human brains that is not normally available to conscious awareness.

Neurological:

In some cases, savant syndrome can be induced following severe head trauma to the left anterior temporal lobe. Savant syndrome has been artificially replicated using transcranial magnetic stimulation to temporarily disable this area of the brain. A neurocognitive model of savant syndrome should explain these cognitive features and the juxtaposition of outstanding talents with cognitive disabilities. In recent neuropsychological studies, Miller (1998) reported clinical cases of "acquired savant," i.e., patients who improved or newly acquired an artistic savant-like skill in the early stage of frontotemporal dementia (FTD). Although the relationship between an autistic savant and acquired savant remains to be elucidated, the advent of neuroimaging study of ASD and the clarification of FTD patients with savant-like skills may clarify the shared neural mechanisms of both types of talent.

Genetical information of Savant syndrome:

There are not many published data about it but it is a rare single nucleotide mutation. So we tried to find the gene for the savant syndrome and successfully we found that GABRB3 was the gene mutated which caused the syndrome. It is related to the chloride gated channel in nervous system.

Treatment for Savant syndrome:

Savant syndrome is diagnosed when a child's ability in one area is exceptionally higher than would be expected given his or her IQ or general level of functioning. Savant syndrome is not known to have any drawbacks, so it does not have to be treated itself. The underlying disorders that usually accompany savant

syndrome need to be treated, and it is believed that making use of the special talent of the child with savant syndrome may help treat the child's underlying developmental disorders. The special skill associated with savant syndrome in a specific child is usually present for life. There has been at least one report of the skill being lost when progress was gained in other areas, but this appears to be very rare. In general, if the level of the skill changes it improves as the skill is practiced. There is no known way to prevent savant syndrome.

CHAPTER-2

LITERATURE SURVEY

2.1 Books that documented Savant syndrome:

✓ The “Gnothi Sauton” published the first documented case with the information of a mathematical prodigy named “Jedediah Buxton”, who was able to perform calculations in his head with remarkable speed.

✓ This syndrome came in to light among many civilians after the release of some books that were inspired from Dr.Down’s publication. Some of books are:

✓ In 1989, Extraordinary people was first published by Treffert, summarizing a century of cases, observations and research findings since Down's 1887 description of the disorder.

✓ Beate Hermelin, in her book, “Bright splinters of the mind”,(2001) summarized her findings based on 20 years of research by her and her co-workers.

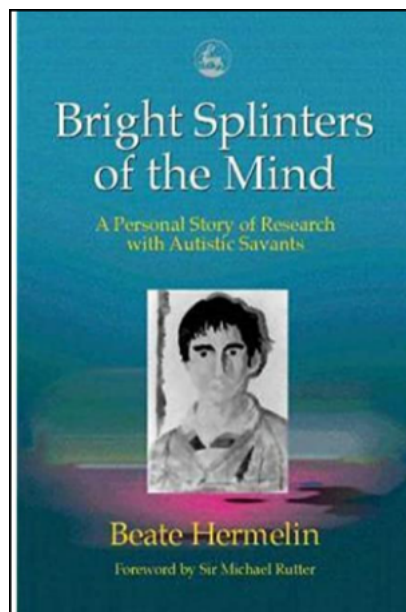


Fig 2.1(a)

Bright splinters of the mind.

✓ A comprehensive review article by Heaton & Wallace (2004) also provides an extensive bibliography on research to that date.

1. The referred publication is "*Encyclopedia of children's health*" which provides the detail information of the syndrome and also the user contribution which provides the detail and more closer exposure of the syndrome in real time and also people impression on the syndrome in different parts of the world and the basic education which is enough to understand the syndrome for the not biological background people. It helped us in a great way to understand the syndrome and how is it different from the rest of the mental disorders. It paved a path to the interest for this project.

2. Treffert described a blind, autistic musical savant who, along with her musical ability, demonstrated very precise spatial location abilities and precise time-keeping skills without access to a clock face or other time instruments. Detailed reports of these and many other savants dating from Down's original description of the disorder are contained in "Extraordinary people: understanding savant syndrome (Treffert)" Which gives the more modern approach of the author to the specific topic and is better explained in detail.

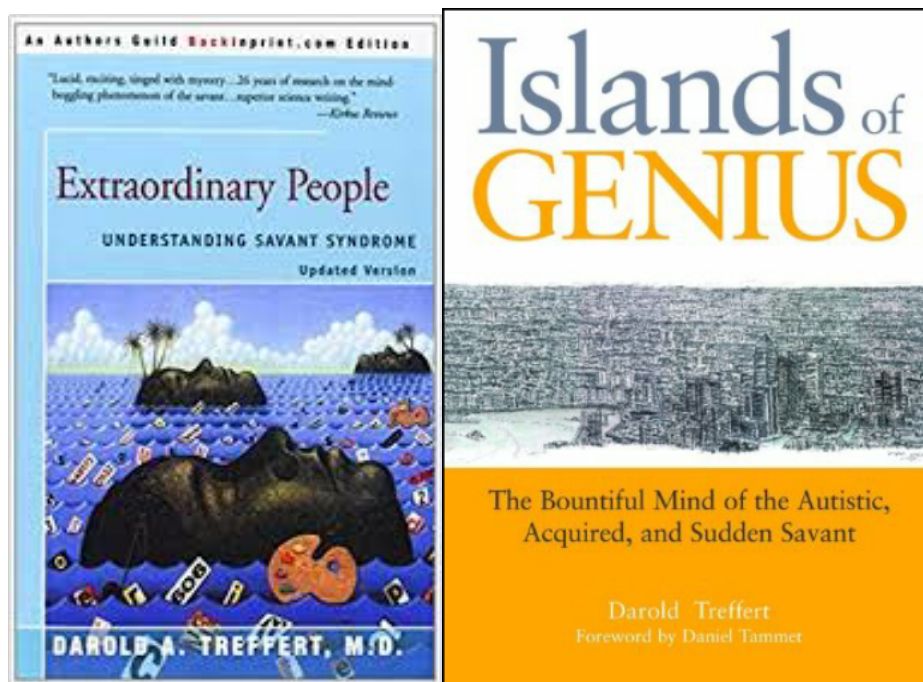


Fig 2.1.2(a&b)

The books written by Darold Treffert.

3. Without doubt, the best-known autistic savant is a fictional one, "Raymond Babbitt", as portrayed by Dustin Hoffman in the 1988 movie Rain man. However, the original inspiration for the savant portrayed in Rain man was a now 57-year-old

male who has memorized over “6000 books” and has encyclopedic knowledge of geography, music, literature, history, sports and nine other areas of expertise. He can name all the US area codes and major city zip codes. He has also memorized the maps in the front of telephone books and can tell you precisely how to get from one US city to another, and then how to get around in that city street by street. He also has calendar-calculating abilities and, more recently, rather advanced musical talent has surfaced. Of unique interest is his ability to read extremely rapidly, simultaneously scanning one page with the left eye and the other page with the right eye. Magnetic resonance imaging (MRI) shows the “absence of the corpus callosum” along with other substantial central nervous system (CNS) damage. This book is the detail given by the autistic savant person himself so the details are predominant with a more close approach and to understand them in a personal way.

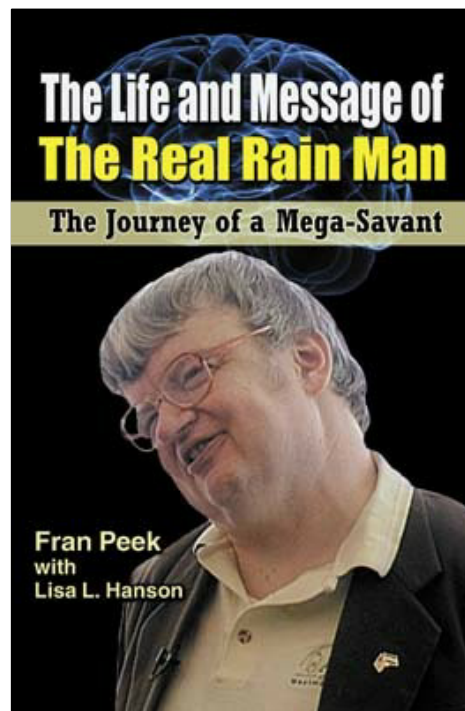


Fig 2.1.3(a)

Written by the Fran Peek.

The absence of the corpus callosum is called ACC, it is a rare disorder that is present at birth (congenital). It is characterized by a partial or complete absence (agenesis) of an area of the brain that connects the two cerebral hemispheres. This part of the brain is normally composed of transverse fibers. In some cases mental retardation may result, but intelligence may be only mildly impaired and subtle

psychosocial symptoms may be present. They are usually connected with other psychological disorders and in this case it is “autistic savant”.

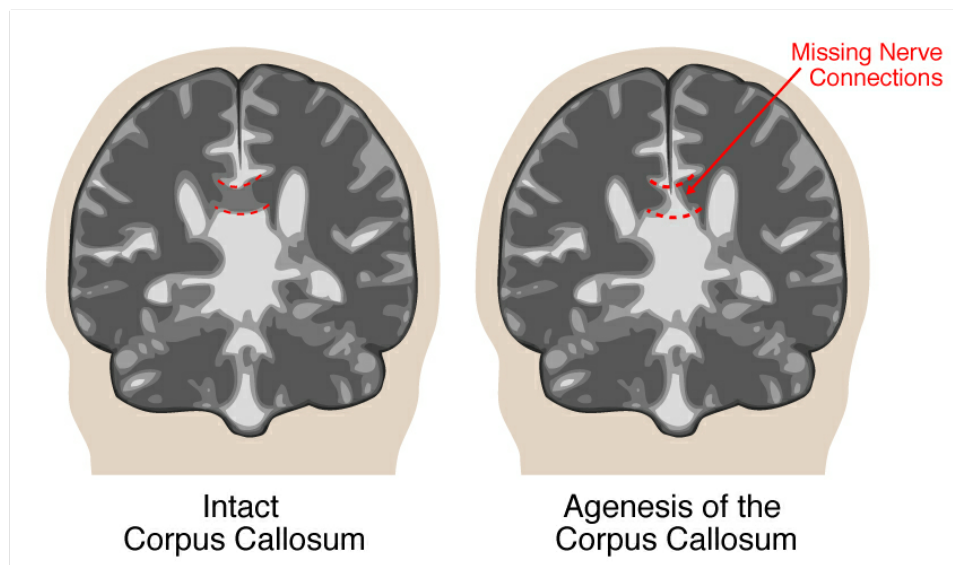


Fig 2.1.3(b)

Difference between ICC and ACC.

2.2 The articles related to savant syndrome:

1.) The savant syndrome: an extraordinary condition. A synopsis: past, present, future.

Darold A. Treffert (University of Wisconsin Medical School.)

Savant syndrome is a rare, but extraordinary, condition in which persons with serious mental

disabilities, including autistic disorder, have some 'island of genius' which stands in marked,

incongruous contrast to overall handicap. As many as one in 10 persons with autistic disorder have such remarkable abilities in varying degrees, although savant syndrome occurs in other

developmental disabilities or in other types of central nervous system injury or disease as well.

Whatever the particular savant skill, it is always linked to massive memory. This paper presents a brief review of the phenomenology of savant skills, the history of the concept and implications for education and future research.

2.) Savant Syndrome: Realities, Myths and Misconception

Darold A. Treffert (Agnesian HealthCare)

It was 126 years ago that Down first described savant syndrome as a specific condition and 70 years ago that Kanner first described Early Infantile Autism. While as many as one in ten autistic persons have savant abilities, such special skills occur in other CNS conditions as well such that approximately 50 % of cases of savant syndrome have autism as the underlying developmental disability and 50 % are associated with other disabilities. This paper sorts out realities from myths and misconceptions about both savant syndrome and autism spectrum disorders (ASD) that have developed through the years. The reality is that low IQ is not necessarily an accompaniment of savant syndrome; in some cases IQ can be superior. Also, savants can be creative, rather than just duplicative, and the skills increase over time on a continuum from duplication, to improvisation to creation, rather than diminishing or suddenly disappearing. Genius and prodigy exist separate from savant syndrome and not all such highly gifted persons have Asperger's Disorder. This paper also emphasizes the critical importance of separating 'autistic-like' symptoms from ASD especially in children when the savant ability presents as hyperlexia (children who read early) or as Einstein syndrome (children who speak late), or have impaired vision (Blindisms) because prognosis and outcome are very different when that careful distinction is made. In those cases the term 'outgrowing autism' might be mistakenly applied when in fact the child did not have ASD in the first place.

3.)The savant syndrome :Genius and mental handicap combined.

J. A. M. SCHIPPERHEIJN, Locum Senior Registrar in Psychiatry, Napsbury Hospital,

Herts; and F. J. DUNNE, Consultant Psychiatrist, Warley Hospital, Brentwood.

Idiot-savants are people of low intelligence who have one or two outstanding talents such as calendar calculation, drawing, or musical performance. The syndrome occurs with high frequency among autistic children (autism is about four times commoner in boys), and the male to female ratio is about 6:1 suggesting a sex linked disorder (Hill, 1977). It is estimated to occur in 0.060/0 of the mentally handicapped population or about 1 in 2,000 of those living in institutions (Treffert, 1988). The gift starts apparently spontaneously between age 5 and 8 years. Frequently the parents claim that they themselves do not have the talent and know of no one in the family who has, but there is a tendency for savant skills to run in families, suggesting that genetic factors play a role. The syndrome was first

described by Langdon Down in 1887 but Tredgold (1914) wrote the first definitive account of the condition. Several types are found: calendar calculators, artists, musicians and mnemonists. The condition can be congenital, or acquired in an otherwise normal individual following injury to or disease of the central nervous system. The skills can appear suddenly and likewise disappear without explanation. Regardless of their particular ability, savants all have in common a phenomenal memory. The term itself is a misnomer being derived from the obsolete definition 'idiot' denoting an individual with an IQ of 25 or below, and the word 'savant' or knowledgeable person from the French 'savoir' meaning, 'to know'. Most savants have a very low IQ, otherwise they would not be classified as such. Communication problems are common and include low-level grammatical grasp, slowness, mutism, complete absence of speech, hesitant speech, withdrawal and autism (O'Connor, 1989). Calendar calculators and savants with mathematical ability and exceptional mnemonic skills are the most frequent; musicians are rare. In some individuals, skills are remarkable because of the associated mental handicap (talented savants); in others (prodigious savants) the abilities would be considered spectacular even if they occurred in normal people. Skills can also occur in combination, for instance, music and memory. Calculators are capable of remarkable feats of mental arithmetic, including the multiplication of three-figure numbers in a few seconds, the rapid calculation of square roots, and the description of a geometric series to 64 places (Hermelin & O'Connor, 1983). They follow simple rules which are used as an aid to recalling dates and sequences in classical music; the skills though impressive may be confined to tonal music. Rule-based strategies are used by all savants and seem to be IQ independent.

4.) Neural Mechanism Underlying Autistic Savant and Acquired Savant Syndrome.

Keisuke Takahata, Motoichiro Kato

Department of Neuropsychiatry, Keio University School of Medicine

It is well known that the cases with savant syndrome, demonstrate outstanding mental capability despite coexisting severe mental disabilities. In many cases, savant skills are characterized by its domain-specificity, enhanced memory capability, and excessive focus on low-level perceptual processing. In addition, impaired integrative cognitive processing such as social cognition or executive function, restricted interest, and compulsive repetition of the same act are observed in savant individuals. All these are significantly relevant to the behavioral

characteristics observed in individuals with autistic spectrum disorders (ASD). A neurocognitive model of savant syndrome should explain these cognitive features and the juxtaposition of outstanding talents with cognitive disabilities. In recent neuropsychological studies, Miller (1998) reported clinical cases of "acquired savant," i.e., patients who improved or newly acquired an artistic savant-like skill in the early stage of frontotemporal dementia (FTD). Although the relationship between an autistic savant and acquired savant remains to be elucidated, the advent of neuroimaging study of ASD and the clarification of FTD patients with savant-like skills may clarify the shared neural mechanisms of both types of talent. In this review, we classified current cognitive models of savant syndrome into the following 3 categories. (1) A hypermnestic model that suggests that savant skills develop from existing or dormant cognitive functions such as memory. However, recent findings obtained through neuropsychological examinations imply that savant individuals solve problems using a strategy that is fairly different from a non-autistic one. (2) A paradoxical functional facilitation model (Kapur, 1996) that offers possible explanations about how pathological states in the brain lead to development of prodigious skills. This model emphasizes the role of reciprocal inhibitory interaction among adjacent or distant cortical regions, especially that of the prefrontal cortex and the posterior regions of the brain. (3) Autistic models, including those based on weak central coherence theory (Frith, 1989), that focus on how savant skills emerge from an autistic brain. Based on recent neuroimaging studies of ASD, Just et al. (2004) suggested the underconnectivity theory, which emphasizes the disruption of long-range connectivity and the relative intact or even more enhanced local connectivity in the autistic brain. All the models listed above have certain advantages and shortcomings. At the end of this review, we propose another integrative model of savant syndrome. In this model, we predict an altered balance of local/global connectivity patterns that contribute to an altered functional segregation/integration ratio. In particular, we emphasize the crucial role played by the disruption of global connectivity in a parallel distributed cortical network, which might result in impairment in integrated cognitive processing, such as impairment in executive function and social cognition. On the other hand, the reduced inter-regional collaboration could lead to a disinhibitory enhancement of neural activity and connectivity in local cortical regions. In addition, enhanced connectivity in the local brain regions is partly due to the abnormal organization of the cortical

network as a result of developmental and pathological states. This enhanced local connectivity results in the specialization and facilitation of low-level cognitive processing. The disruption of connectivity between the prefrontal cortex and other regions is considered to be a particularly important factor because the prefrontal region shows the most influential inhibitory control on other cortical areas. We propose that these neural mechanisms as the underlying causes for the emergence of savant ability in ASD and FTD patients.

5.) Neurophenomenology of Savant syndrome.

Dito Anurogo(Brain Circulation Institute of Indonesia (BCII)),Taruna Ikrar(School of Medicine, University of California)

Savant syndrome is an enigmatic disorder. It is characterized by cluster of outstanding mental ability in otherwise handicapped individuals. People with savant syndrome exhibit exceptional-extraordinary abilities and demonstrate some specific talents or particular skills along with developmental disabilities. Their profound and prodigious abilities are far in excess of what are considered normal. There is a paradoxical presence of special skills and distinguished disabilities. The documented savant skills include “lightning-speed” numerical calculation, calendrical calculation, musical savants (exceptional musical abilities, especially perfect pitch), artistic skills, hyperlexics (fast reading and understanding). Other types of talents and artistic skills involving three-dimensional drawing, map memory, poetry, painting, and sculpturing are also observed. The goal of this scientific article is to review savant syndrome, based on neurophenomenology framework and recent findings.

6.)Savant syndrome - Theories and Empirical findings

Helene Darius (University of Skövde, Sweden) Institution of Communication and Information , Katja Valli(University of Turku, Finland)Centre of Cognitive Neuroscience

Savant syndrome is a rare condition in which some people have extraordinary talents despite some serious mental or physical disability. It is a syndrome with remarkable features, standing in stark contrast to a person’s overall character. The term savant, or idiot savant, describes a person who, in spite of low intelligence, has a skill in some specific narrow area. Savants can have a specific talent in, for instance, music, art, calendar calculation or foreign language but whatever the specific talent is, it is always connected to extraordinary memory. Savant syndrome

seems to be also connected to autism or autistic characteristics. In this paper I aim to give a clear description of the savant syndrome and explain its connection to autism. Further, I present how specific theories try to describe the causes of savant syndrome, and connect the theories to results of empirical research in order to give an overall view of the syndrome's appearance. I will also compare the theories and evaluate their strengths and weaknesses with respect to the discoveries and progress that has been made within the area of savant syndrome research.

7.)Autworks: a cross-disease network biologyapplication for Autism and related disorders.

**Tristan H Nelson, Jae-Yoon Jung, Todd F DeLuca, Byron K Hinebaugh,
Kristian Che St. Gabriel and Dennis P Wall**

Autism spectrum disorder (ASD) is one of the most common and highly heritable neurodevelopmental disorders. Despite, and perhaps because of, its commonality, ASD is known to have a highly complex genetic etiology. More than 100 genes have been reported to be perturbed in individuals with ASD, while only a few such genes have been verified by genome-wide association studies or gene expression analyses. There are a number of Mendelian disorders in which patients may manifest ASD traits, including fragile X syndrome, tuberous sclerosis complex, Rett syndrome , and Angelman syndrome to name a few. Finally, common copy number variations have been found between ASD and other complex mental disorders, including schizophrenia, bipolar disorder , and epilepsy .The complexity of the autism genetic landscape suggests that networks of candidate genes will be of value to identify biological themes that contribute to the spectrum of autism phenotypes. Innovative work by Rzhetsky et al. demonstrated that significant correlations of comorbidity were found across a wide range of disorders, ASD in particular. Related research demonstrated that combining the known genetic etiology of behaviorally related disorders with ASD through biological networks could provide particular insight into genes with great significance in ASD, as well as predictive power for novel autism-associated variants .To capitalize on the value of network biology and a cross-disease understanding of autism, we built a web application called Autworks to allow for network scale cross-disorder analysis. We aimed to integrate pathogenic and genomic information spread across different data repositories and to augment this with novel features including network analysis and visualization tools lacking in existing application.

8.)AutismKB 2.0: a knowledgebase for the genetic evidence of autism spectrum disorder.

Changhong Yang, Jiarui Li, Qixi Wu, Xiaoxu Yang, August Yue Huang, Jie Zhang, Adam Yongxin Ye, Yanmei Dou, Linlin Yan, Wei-zhen Zhou, Lei Kong, Meng Wang, Chen Ai, Dechang Yang and Liping Wei.

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder with strong genetic contributions. To provide a comprehensive resource for the genetic evidence of ASD, we have updated the Autism KnowledgeBase (AutismKB) to version 2.0. AutismKB 2.0 integrates multiscale genetic data on 1379 genes, 5420 copy number variations and structural variations, 11 669 single-nucleotide variations or small insertions/deletions (SNVs/indels) and 172 linkage regions. In particular, AutismKB 2.0 highlights 5669 de novo SNVs/indels due to their significant contribution to ASD genetics and includes 789 mosaic variants due to their recently discovered contributions to ASD pathogenesis. The genes and variants are annotated extensively with genetic evidence and clinical evidence. To help users fully understand the functional consequences of SNVs and small indels, we provided comprehensive predictions of pathogenicity with iFish, SIFT, Polyphen etc. To improve user experiences, the new version incorporates multiple query methods, including simple query, advanced query and batch query. It also functionally integrates two analytical tools to help users perform downstream analyses, including a gene ranking tool and an enrichment analysis tool, KOBAS. AutismKB 2.0 is freely available and can be a valuable resource for researchers.

Database URL: <http://db.cbi.pku.edu.cn/autismkb v2>

9.)Single nucleotide polymorphisms predict symptom severity of autism spectrum disorder.

Yun Jiao, Rong Chen and Edward H Herskovits.

Autism is widely believed to be a heterogeneous disorder; diagnosis is currently based solely on clinical criteria, although genetic, as well as environmental, influences are thought to be prominent factors in the etiology of most forms of autism. Our goal is to determine whether a predictive model based on single-nucleotide polymorphisms (SNPs) can predict symptom severity of autism spectrum disorder (ASD). We divided 118 ASD children into a mild/moderate autism group (n = 65) and a severe autism group (n = 53), based on the Childhood Autism Rating Scale (CARS). For each child, we obtained 29 SNPs of 9 ASD-related

genes. To generate predictive models, we employed three machine-learning techniques: decision stumps (DSs), alternating decision trees (ADTrees), and FlexTrees. DS and FlexTree generated modestly better classifiers, with accuracy = 67%, sensitivity = 0.88 and specificity = 0.42. The SNP rs878960 in GABRB3 was selected by all models, and was related associated with CARS assessment. Our results suggest that SNPs have the potential to offer accurate classification of ASD symptom severity.

10.)A review of Savant Syndrome and its possible relationship to epilepsy.

John R. Hughes

The goal of this article is to review Savant Syndrome, characterized by outstanding islands of mental ability in otherwise handicapped individuals. Two forms exist: the congenital form and the acquired form. Among the many examples of the congenital form are the calendar calculators, who can quickly provide the day of the week for any date in the past; the musical savants, who have perfect pitch; and the hyperlexics, who (in one case) can read a page in 8 s and recall the text later at a 99% level. Other types of talents and artistic skills involving three-dimensional drawing, map memory, poetry, painting, and sculpturing are also observed. One savant could recite without error the value of Pi to 22,514 places. Persons with the acquired form develop outstanding skills after brain injury or disease, usually involving the left frontotemporal area. This type of injury seems to inhibit the “tyranny of the left hemisphere,” allowing the right hemisphere to develop the savant skills. Another way to inhibit the left frontotemporal area is to use transcranial magnetic stimulation in normal subjects; nearly one-half of these subjects can then perform new skills during the stimulation that they could not perform before. This type of finding indicates the potential in all of us for the development of savant skills in special circumstances. Explanations of congenital Savant Syndrome include enhanced local connectivity as a compensation for underconnectivity of long-range fibers, but also weak central coherence, replaced by great attention to detail, enhanced perceptual functioning, and obsessive preoccupation with specific interests.

CHAPTER- 3

AIM & SCOPE

3.1 AIM

To acquire the pathway for the neurodevelopmental disorder by analyzing the data using computational approaches like the bioinformatic tools.

3.1.1 Existing system:

In the past decade, particularly, much progress has been made towards explaining this jarring juxtaposition of ability and disability, but many unanswered questions remain. However, interest in this fascinating condition is accelerating, especially since the discovery of savant-type skills in previously unimpaired older persons with FTD and other acquired savant instances. This finding has far-reaching implications regarding buried potential in some or, perhaps, all of us.

Advanced technologies will help in those investigations. Computed tomography (CT) and MRI provide stunningly high-resolution images of all the brain architecture, surface and deep, permitting detailed inspection of brain structure. However, studies of brain function, such as positron emission tomography (PET), single photon emission CT (SPECT) or functional MRI, are much more informative regarding savant syndrome, and, indeed, autism itself, since these newer techniques provide information about the brain at work, rather than simply viewing brain architecture. An even more recent imaging technique is diffusion tensor imaging, based on measuring water flow within neurons, which provides graphic images of brain connectivity between the brain hemispheres, within the brain hemispheres and between upper cortical and lower brain stem structures. A related technique, diffusion tensor tracking, provides a direct visual view of the actual fibre tracks, or wiring, of the brain in great detail.

3.1.2 Motivation :

The savant is a rare yet seen among the autistic patients. In every 100 autistic there are 1 to 10 patients with savant syndrome yet are not recognized among the parents and even teachers due to lack of the knowledge about this condition and do not take any further care to help the children. We personally went volunteer in a school specially for the autistic children and studied about their personality and the

type of education needed for them and realized to take this syndrome as the main subject for our project.

3.1.3 Proposed System:

In the work we use different biological tools and databases to find the main genetic resource and the reasoning for the syndrome and connect many broken parts to form a pathway and prove that they are normal and even more extraordinary to all the readers of this documentation.

As the required genes is related to the Savant syndrome we used SFARI Gene to collect the data. Simons Foundation Autism Research Initiative is the foundation that was established in 2005, there after this is converted in to a free web portal with the information about Autistic disorders. The genes related to savant syndrome is collected from Sfari,a autism related web portal.The genes is GABRB3gamma-aminobutyric acid (GABA) A receptor, beta 3.

3.2 SCOPE OF THE PROJECT:

Our main scope is to Reconstruct the pathway of the Savant syndrome and use network biology to compare the genes that have undergone the mutations which affect function the protein and enzyme reactions.

CHAPTER - 4

EXPERIMENTAL

4.1 ARCHITECTURE DIAGRAM:

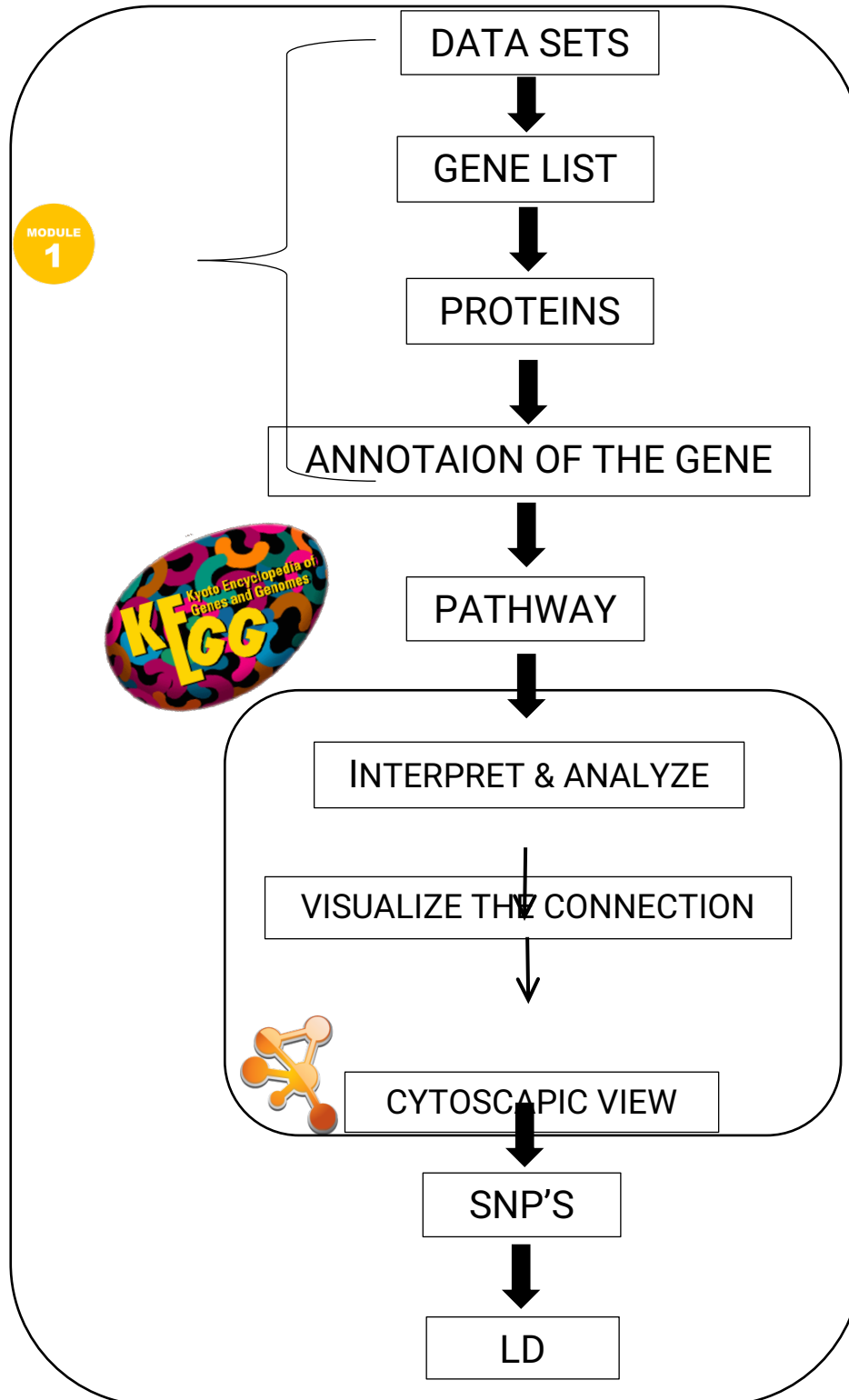


FIG 4.1

ARCHITECTURE DIAGRAM

Savant syndrome is a neurodevelopmental problem faced due to a rare single nucleotide mutation and is a chloride channel related problem and can only be proved by following the steps mentioned in fig 4.1. Each of these steps contain a form of sequential process following them. The process is completed using different and only bioinformatic tools. The mathematical calculations are done for SNP's and LD's which will be explained in the later parts of the report.

The genes related have been taken from the existing database sources. It is not easy to find the information about them. The pathway gives a clear view about the genes related which in turn will help in finding the related SNP's and relate them to the different populations of the world using LD.

4.2 SYSTEM REQUIREMENT

The project will require some software and hardware to develop the system and these

resources are mandatory to develop the project with utmost accuracy. The hardware

and software required to develop the proposed system are listed below:

4.3 HARDWARE REQUIREMENTS

Hardware specifications are technical description of the computer's components and capabilities. Processor speed, model and manufacturer, etc. so the hardware components required for the proposed system are:

- Processor : Intel Core i5.
- Hard disk : 1TB.
- Speed : 2.4GHz
- Memory : 4 GB

4.4 SOFTWARE REQUIREMENT:

A software requirement specification is a description of a software system to be developed. It lays out functional and non-functional requirements and it also describes

the operating system and tool used in the system and they are:

- Operating system : Any (Java-based)
- Written in : Java.

CHAPTER -5

RESULTS AND DISCUSSION.

5.1 MODULE-1:

Data Sets is the collection of the genetic information in a more precise way, but it is the collection of the query data. It involves the required information about the savant syndrome which was derived from the exclusive database for the savant, autism and other neurodevelopmental disorders. It is run by a foundation which does research on the mentioned disorders. As the required genes are related to the Savant syndrome we used SFARI Gene to collect the data. Simons Foundation Autism Research Initiative is the foundation that was established in 2005, thereafter this is converted into a free web portal with the information about Autistic disorders.

The genes related to savant syndrome are collected from Sfari, an autism-related web portal.

SFARI -

- The database that has information about genes associated with ASD.
- This DB has several external genetic database links, includes data from various animal models provides the information that can be used to identify the mechanisms of ASD.
- Protein interaction(PIN) module gives interactive visual reference that shows all known protein interactions of genes associated to ASD
- Provides the data on all known copy number variants(CNV's) associated to ASD and many more.

The screenshot shows the SFARI GENE database interface. At the top is a blue navigation bar with links: SFARI GENE, DATABASE, ABOUT, TOOLS, USER GUIDE, NEWS, and ARCHIVE. Below the navigation bar, the search results for 'savant' are displayed. A filter bar shows 'All (1)', 'Human Genes (1)', 'Copy Number Variants (0)', and 'Mouse Models (0)'. The main result is for the gene **GABRB3**, identified as a 'HUMAN GENE - CHROMOSOME 15'. It shows 'AUTISM REPORTS / TOTAL REPORTS' as '21 / 37' and a 'GENETIC CATEGORY' of 'Rare Single Gene Mutation, Genetic Association'. A yellow 'SCORE 2' badge is visible. A section titled 'FROM RELEVANCE-TO-AUTISM' contains text stating: 'As well, a number of studies have found genetic association between the GABRB3 gene and autism (including one that enriched for savant skills)'.

FIG 5.1 (a)
SFARI GENE QUERY.

The genes are categorised based on:

CATEGORY 1(HIGH CONFIDENCE): Genes in this category are all found on the SPARK gene list, or on the list of genes reported by Satterstrom et al., Cell 180, 1-17 (2020). Each of these genes has been clearly implicated in ASD—typically by the presence of at least three de novo likely-gene-disrupting mutations being reported in the literature—and such mutations identified in the sequencing of the SPARK cohort are typically returned to the participants. Some of these gene meet the most rigorous threshold of genome-wide significance; all at least meet a threshold false discovery rate of < 0.1

CATEGORY 2(STRONG CANDIDATE):Genes with two reported de novo likely-gene-disrupting mutations.A gene uniquely implicated by a genome-wide association study, either reaching genome-wide significance or, if not, consistently replicated and accompanied by evidence that the risk variant has a functional effect.

Strong Candidate	AUTISM REPORTS / TOTAL REPORTS	RARE VARIANTS / COMMON VARIANTS
Score - 2	21 / 37	47 / 29

ALIASES	ASSOCIATED SYNDROMES	GENETIC CATEGORY
GABRB3, MG C9051	-	Rare Single Gene Mutation, Genetic Association

CHROMOSOME BAND	ASSOCIATED DISORDERS	CRITERIA
15q12	ADHD, ASD, ID, DD/NDD	1.1

TAB 4.4.1(a)
SFARI GENE INFORMATION.

MOLECULAR FUNCTION : The encoded protein is a subunit of GABA-A receptor. Neurotransmission is predominantly mediated by a gated chloride channel activity intrinsic to the receptor.

EXTERNAL LINKS: SFARI provides the several external links for the query gene. It is according to the required experimental subject database. Gene cards, OTP, PubMed are the basic external links. The human related database are Entrez Gene, OMIM, Uniprot, HumanBase. The mouse related data for the savant are from Entrez Gene, Mouse Genome Informatics, Allen Brain Atlas. The experimental subject information of fruit fly is Entrez Gene.

Ensembl:	ENSG00000166206
MIM:	137192
HGNC:	HGNC:4083
Vega:	OTTHUMG00000129231
Entrez:	2562
UniProtKB:	P28472
UniProtKB:	X5DQY4
UniProtKB:	B2RCW8
Gtex:	GABRB3
SFARI-Gene:	GABRB3

FIG 5.1(b)
EXTERNAL LINKS FOR GABRB3.

GENE CARDS: GeneCards is a database of human genes that provides genomic, proteomic, transcriptomic, genetic and functional information on all known and predicted human genes. It is being developed and maintained by the Crown Human Genome Center at the Weizmann Institute of Science. GABRB3 gene encodes a member of the ligand-gated ionic channel family. The encoded protein is one the subunits of a multi-subunit chloride channel that serves as the receptor for gamma-aminobutyric acid, a major inhibitory neurotransmitter of the mammalian nervous system. This gene is located on the long arm of chromosome 15 in a cluster with two other genes encoding related subunits of the family. This gene may be associated with the pathogenesis of several disorders including Savant Syndrome, Angelman syndrome, Prader-Willi syndrome, nonsyndromic orofacial clefts, epilepsy and autism.



FIG 5.1(c)
LOCATION OF GABRB3 (Ch15).

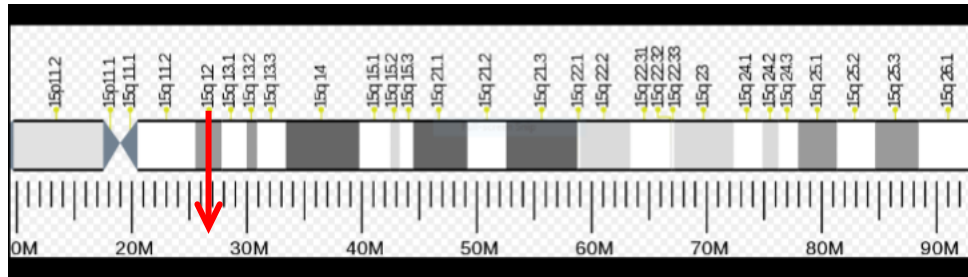


FIG 5.1(d)
EXACT LOCATION OF GABRB3 (Ch15q12).

HUMAN BASE: HumanBase is a “one stop shop” for biological researchers interested in data-driven predictions of gene expression, function, regulation, and interactions in human, particularly in the context of specific cell types/tissues and human disease.

This resource is not merely a public database of primary genomics data or biological literature. The data-driven integrative analyses presented in HumanBase are especially powerful because they separate signal from noise in large biological data collections to reach beyond “existing biological knowledge” represented in the biological literature to identify novel associations that are not biased toward well-studied areas of biomedical research. Thus, HumanBase is a resource for biomedical researchers to incorporate into their research workflows, which they can use to interpret their experimental results and generate hypothesis for experimental follow-up.

HumanBase is actively developed by the Genomics group at the Flatiron Institute.

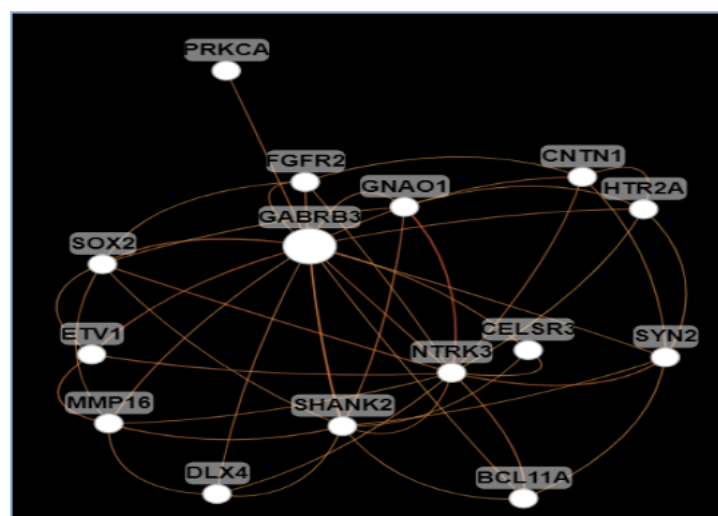


FIG 5.1(e)
Tissue-specific interactions.

The fig 4.4.1(h) is the description of the *tissue specific interaction* in brain.

brain : The portion of the vertebrate central nervous system that constitutes the organ of thought and neural coordination, includes all the higher nervous centers receiving stimuli

The tissue interaction is done based on the co-expression,interaction,TF binding,GSEA microRNA targets and GSEA perturbation.

NAME	DATABASE	GENES	PVALUE
positive regulation of MAPK cascade	Gene Ontology (BP)	4	3.1e-2
positive regulation of phospholipase activity	Gene Ontology (BP)	2	4.4e-2
learning or memory, Gene Ontology (BP)	Gene Ontology (BP)	2	4.4e-2
regulation of phospholipase activity	Gene Ontology (BP)	2	4.4e-2
positive regulation of lipase activity	Gene Ontology (BP)	2	4.6e-2

TAB-5.1(b) Enriched function

This table is the complete information about the Enriched function of the brain in a process. Biological processes and diseases represented in the network.

Tissue expression: Experimentally validated and computationally predicted tissue/cell-type expression

TISSUE	GABRB3 Confidence level
brain	0.95
telencephalon	0.94
nervous system	0.94
central nervous system	0.93
cerebellum	0.93
occipital lobe	0.93
temporal lobe	0.93
frontal lobe	0.93
forebrain	0.92

caudate putamen	0.92
thalamus	0.91
basal ganglion	0.91
diencephalon	0.91
cerebral cortex	0.91
corpus striatum	0.90
caudate nucleus	0.89
midbrain	0.89
amygdala	0.89
substantia nigra	0.88
hippocampus	0.87
subthalamic nucleus	0.84
corpus callosum	0.83
medulla oblongata	0.83
spinal cord	0.80
dentate gyrus	0.80
occipital pole	0.75
fetus	0.55
cerebellar cortex	0.54
hypophysis	0.52
pancreas	0.51
ovary	0.49
testis	0.47
neuron	0.42
kidney	0.41
placenta	0.39
cerebellar Purkinje cell	0.36
prostate gland	0.36
liver	0.36
nucleus accumbens	0.33
pons	0.32
parietal lobe	0.27
thyroid gland	0.24

heart	0.24
adrenal gland	0.21
mammary gland	0.21
hypothalamus	0.20
lung	0.20
gastrointestinal tract	0.20
uterus	0.17
intestine	0.15
retina	0.14
skeletal muscle	0.13
lymph node	0.12
large intestine	0.12
eye	0.12
small intestine	0.11

TAB-5.1(c)

GABRB3 Confidence level.

Each of the confidence level of GABRB3 is calculated for the specific tissue so as to know the amount of the effect that may occur in the specific tissue using the confidence level it may vary from a individual to another. It mainly depends on the patient. This confidence level also proves the existence of the effect even in the fetal stage with a chance of 55% if either one of the parent is a savant syndrome effected or is a carrier of this mutated gene. The confidence is given from 0 to 1 the highest is 1 while 0 is the lowest.

Disease associations: Experimentally associated and computationally predicted associations.

NAME	IDENTIFIER	GABRB3 CONFIDENCE
autism spectrum disorder	DOID:0060041	0.80
epilepsy	DOID:1826	0.23
movement disease	DOID:480	0.20
retinal disease	DOID:5679	0.11

TAB-5.1(d)

Disease associated with GABRB3 and their confidence level

OIMM:

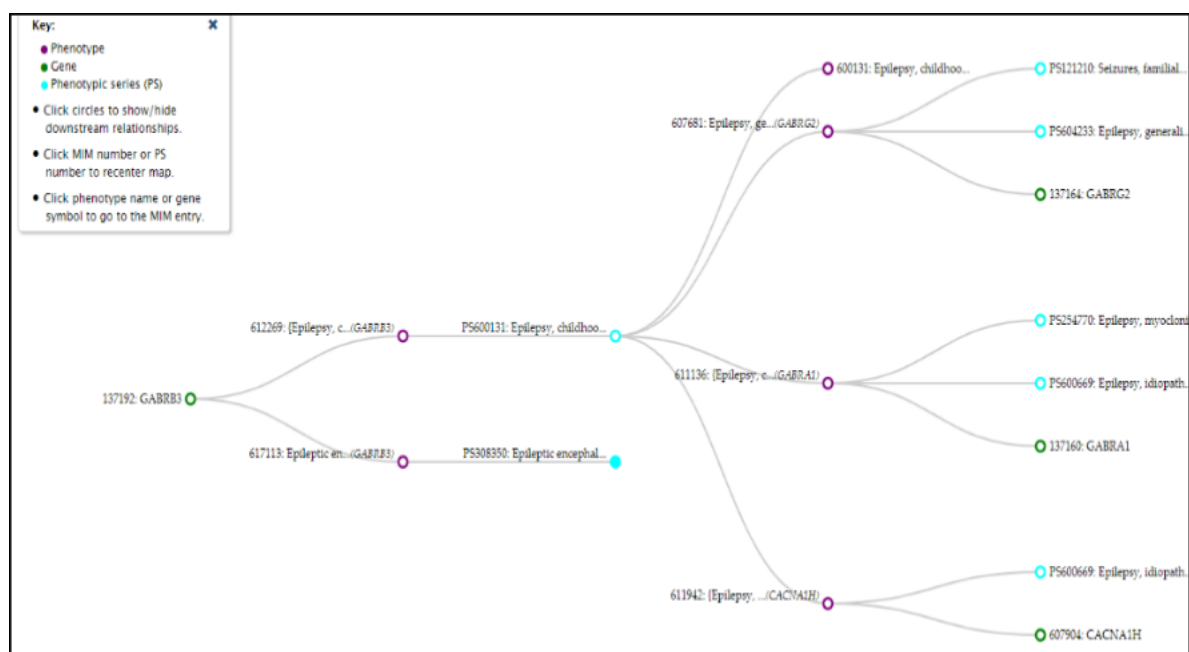


FIG 5.1(f)

PHENEGENE GRAPHICS.

Graphical representation of phenotype/gene relationship(s) associated with the GABRB3. Phenotypic Series (when available) are displayed with the relevant genes and subsequent phenotypes to a depth of 4 nodes. No hierarchy is implied. The graphics represents the childhood related information about the savant syndrome pathway in a graphical way.

PATHWAY:

5.2 PATHWAY Analysis:

The Pathway of the gene is given by the in the form of six pathways in the KEGG. Each of them is significant for each pathway. For the further study the Neuroactive ligand-receptor interaction is taken in to consideration. The other pathways each signifies for one specific functionally related process. This is used to draw a pathway for the gene which can help for the annotating the product according to the requirments.

We have selected the KASS-KEGG for the pathway analysis and it resulted in around six pathways. Each one representing a different yet most accurate pathways.the pathways are shown the fig-5.2(a). The morphine and nicotine an addiction related pathway is also given as the GABA gate effected by it and the rest are the signalling pathways and the GABRB3 that effects is highlighted ina clear way.

We chose Neuroactive ligand-receptor interaction because savant is neurodevelopmental related syndrome and is related to ion gated reaction.

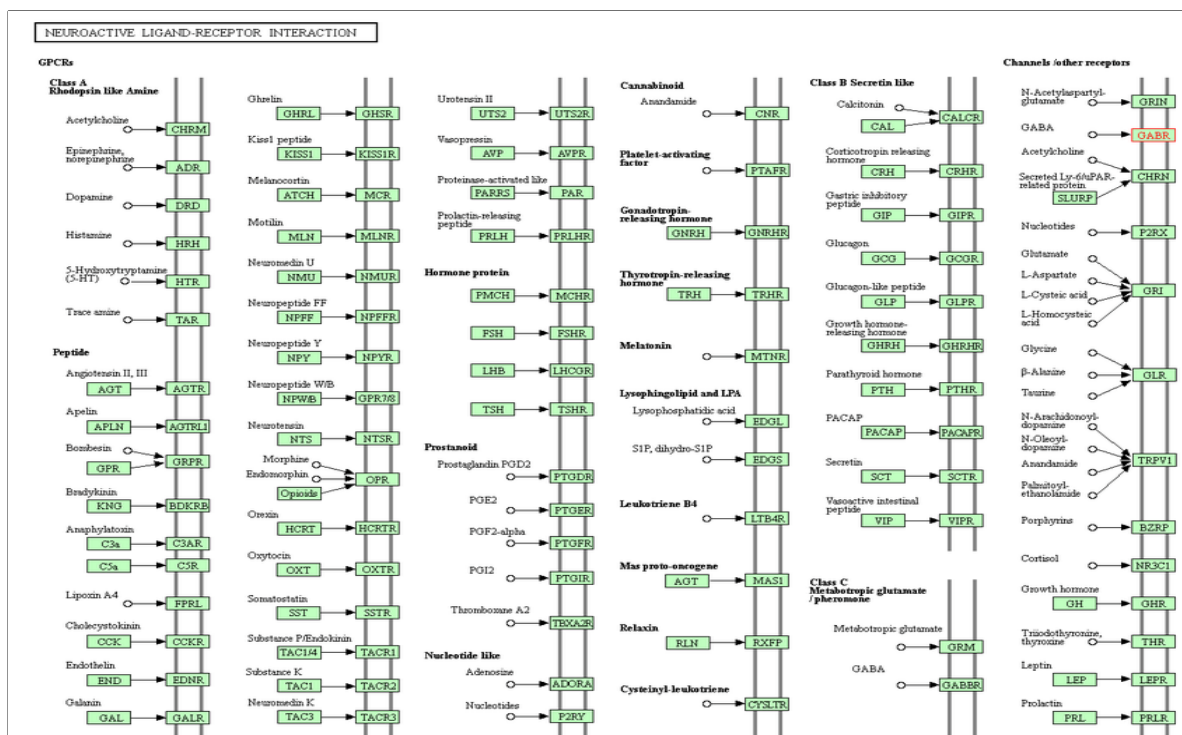
KEGG Homo sapiens (human): 2562			Help
Entry	2562	CDS T01001	
Gene name	GABRB3, ECA5, EIEE43		
Definition	(RefSeq) gamma-aminobutyric acid type A receptor subunit beta3		
KO	K05181 gamma-aminobutyric acid receptor subunit beta		
Organism	hsa Homo sapiens (human)		
Pathway	hsa04080 Neuroactive ligand-receptor interaction hsa04723 Retrograde endocannabinoid signaling hsa04726 Serotonergic synapse hsa04727 GABAergic synapse hsa05032 Morphine addiction hsa05033 Nicotine addiction		
Disease	H00606 Early infantile epileptic encephalopathy H02215 Childhood absence epilepsy		
Drug target	Abecarnil: D02594 Adinazolam (DG00911): D02770 D02771 Adipiplon: D08840 Alpidem: D02833		
			All links Ontology (2) KEGG BRITE (2) Pathway (6) KEGG PATHWAY (6) Disease (5) KEGG DISEASE (2) OMIM (3) Drug (103) KEGG DRUG (103) Genome (1) KEGG GENOME (1) Gene (16) KEGG ORTHOLOGY (1) RefGene (4) NCBI-PROTEINID (1) NCBI-Gene (1) HGNC (1) Ensembl (1) RIKEN BRC-DNA (4) OC (1) PHAROS (1) VEGA (1) Protein sequence (8)

FIG 5.2(b)

KASS-KEGG result for GABRB3.

The figure below has many subunits and one among them has the GABA receptor which channels GABR which is the gene related product for savant.

The reaction is caused due to C4H9NO2 which is gamma-Aminobutyric acid in other words is called GABA



.REACTOME.

This is used to get an overall view about GABRB3 but to analyze and interpret we use reactome. This has the two different pathways:

- ✓ Neuronal system.
- ✓ Signal Transduction.

We choose the Neuronal system as it a brain related syndrome and the plasma membrane is the main thing that is selected.

GABRB3 [plasma membrane]

Stable Identifier	R-HSA-975244
Type	Protein [EntityWithAccessionedSequence]
Species	Homo sapiens
Compartment	plasma membrane
Synonyms	Gamma-aminobutyric acid receptor subunit beta-3, GBRB3_HUMAN

Locations in the PathwayBrowser

- Neuronal System (Homo sapiens)
- Signal Transduction (Homo sapiens)

External Reference Information

External Reference	UniProt:P28472 GABRB3
Gene Names	GABRB3
Chain	signal peptide:1-25, chain:26-473
Reference Genes	BioGPS Gene:2562 GABRB3 COSMIC (genes):GABRB3 GABR... CTD Gene:2562 GABRB3 dbSNP Gene:2562 GABRB3
	ENSEMBL:ENSG00000166206 ... HGNC:4083 GABRB3 KEGG Gene (Homo sapiens):25... Monarch:2562 GABRB3
	NCBI Gene:2562 GABRB3 OMIM:137192 GABRB3 UCSC:P28472 GABRB3
Reference Transcript	RefSeq:NM_001191320.1 GABRB3 RefSeq:NM_001278631.1 GABRB3 RefSeq:NM_000814.5 GABRB3 RefSeq:NM_021912.4 GABRB3 RefSeq:NM_001191321.2 GABRB3
Other Identifiers	0000050086 0004730020 11722663_a_at 11722664_a_at 11722665_a_at 11722666_a_at 11749760_a_at 205850_s_at 227690_at 227830_at 229724_at 2562 31817_at 3614533 3614535 3614536 3614537 3614542 3614546 3614551 3614552 3614562 3614572 3614575 3614566 3614567 3614568 3614569



FIG 5.2(c,d)
Reactome result and the location pathways for GABRB3.

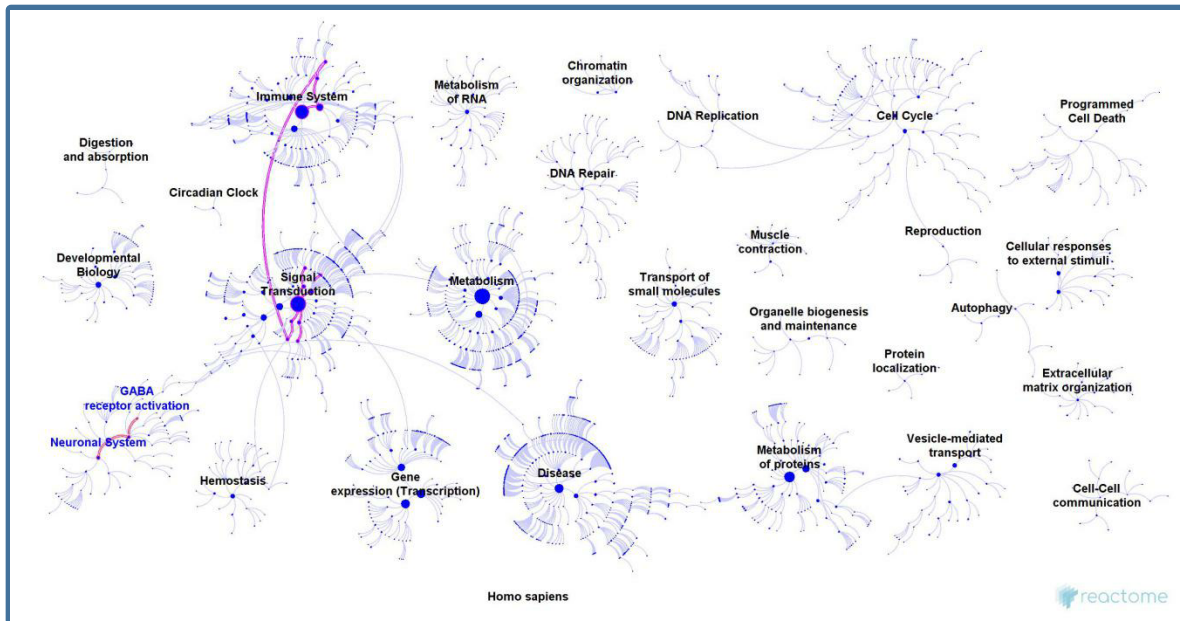


FIG 5.2(f)
Reactome pathway overview for GABRB3.

This is a pathway overview of the GABRB3 of both the neuronal and signal transduction pathways, the GABA receptor and he tissues with relatively more confidence is highlighted accordingly.

The tissue used for the pathway are done according to the confidence mentioned in TAB-4.4.1(c) is used to highlight the locations. Darker the highlight ids directly proportional to the confidence level of GABRB3 in that respective tissue.

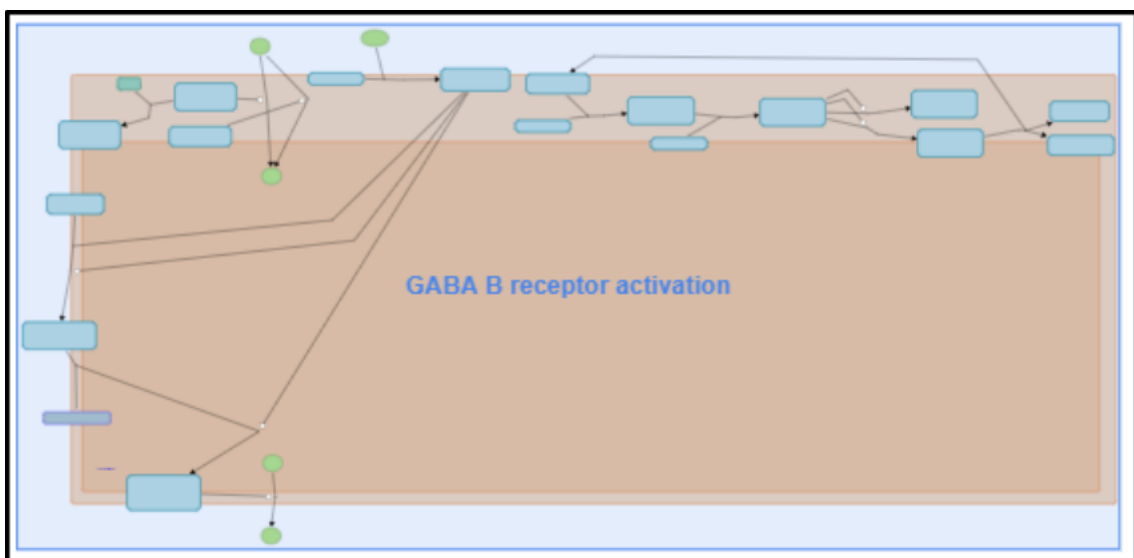


FIG 5.2(g)
Neuronal system pathway.

This is the pictorial pathway for the Neuronal system in specific in the plasma membrane and also shows the ions with a clear view of the receptors on the cell.

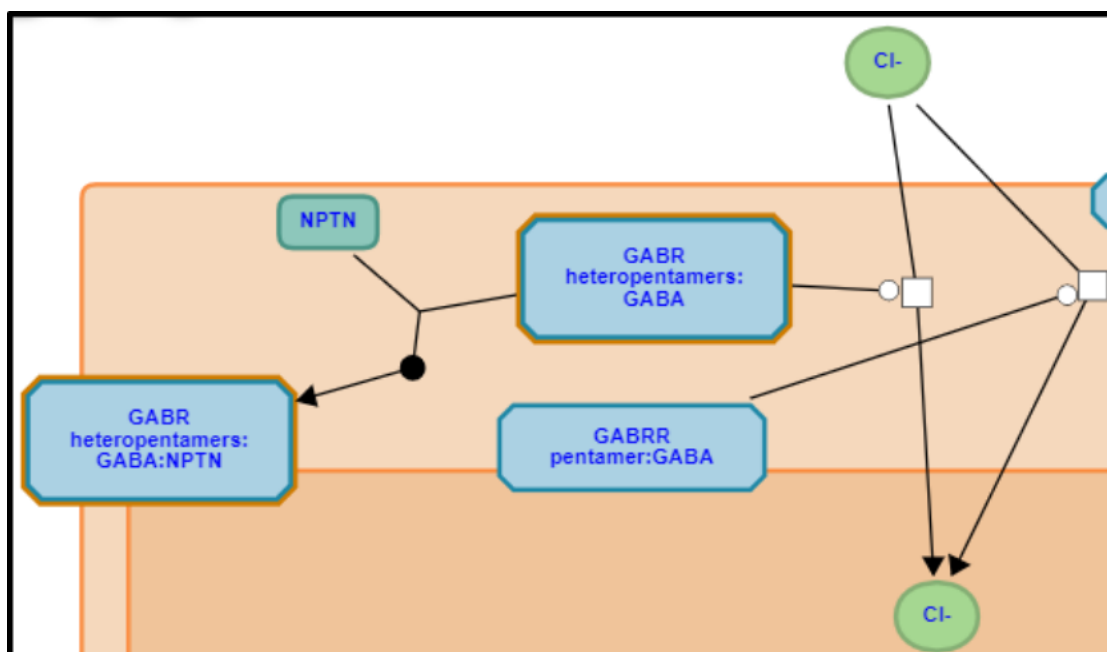


FIG 5.2(h)
Neuronal system of GABA receptor.

This diagram shows that the Cl^- from the extra-cellular region is transported to the cytosol for both heteropentamers GABA and pentamer GABRR. The binding between NPTN (NeuroPlastin) is made clear. The Reactome provides a wide range of options to download and the SBML format is downloaded so as to open it in Cytoscape for further analysis.

CYTOSCAPE:

Cytoscape is an open source bioinformatics software platform for visualizing molecular interaction networks and integrating with gene expression profiles and other state data. Additional features are available as plugins. Plugins are available for network and molecular profiling analyses, new layouts, additional file format support and connection with databases and searching in large networks. Plugins may be developed using the Cytoscape open Java software architecture by anyone and plugin community development is encouraged. Cytoscape also has a JavaScript-centric sister project named "Cytoscape.js" that can be used to analyse and visualise graphs in JavaScript environments, like a browser.

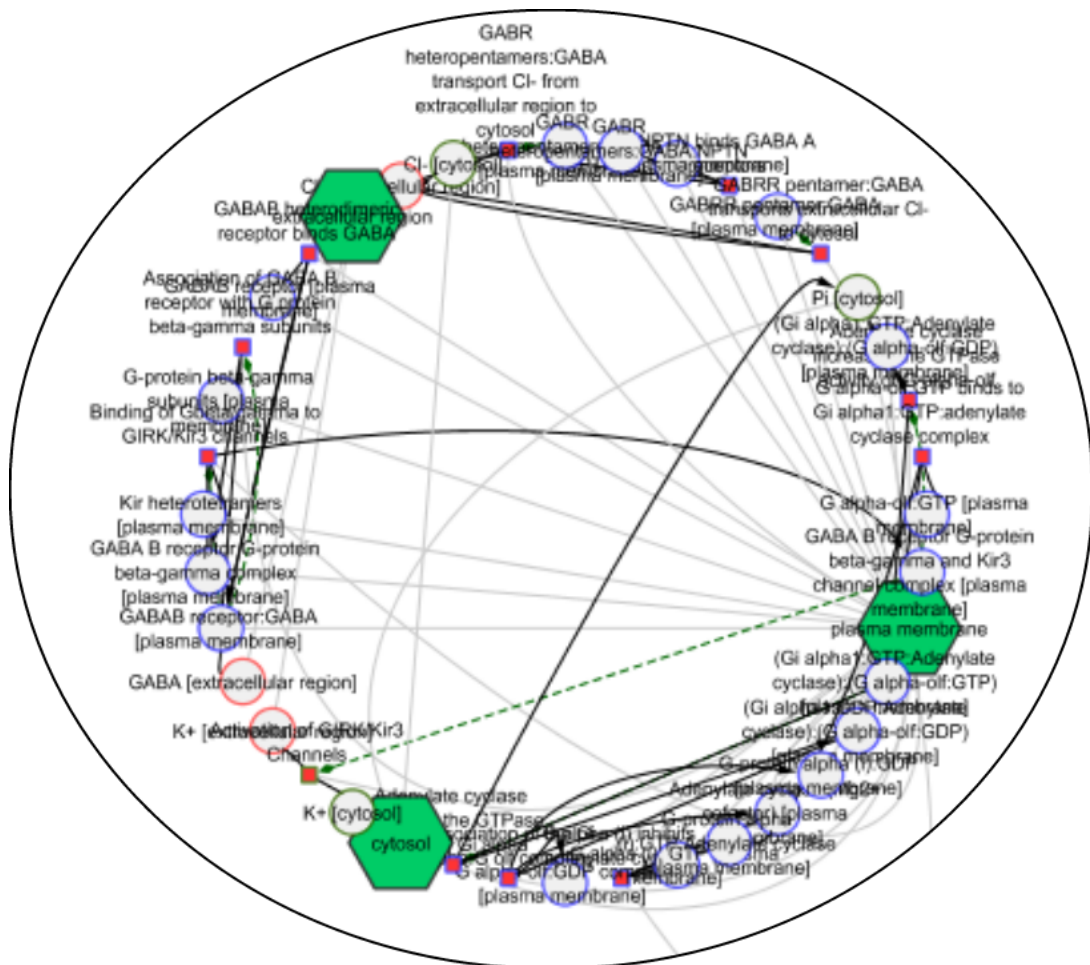


FIG 5.2(i)

Cytoscapic view for GABRB3.

The cytoscape is used to get a more clear view of the pathway.

The network is opened in the cytoscape in the following way
Reactome->pathway->download->SBML format->cytoscape.

The circular view in fig-5.2(i) gives a more approachable understanding of the connections and the products also. The red coloured square box is the spot that highlights the activation channels of GABRB3.

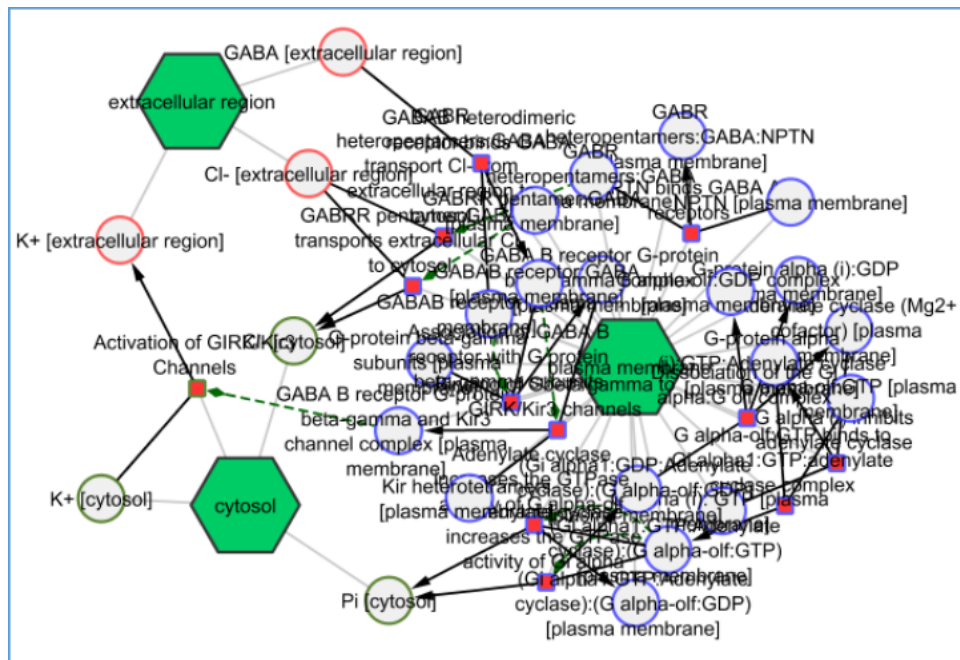


FIG 5.2(i)

Clear view of the activation channels for GABRB3.

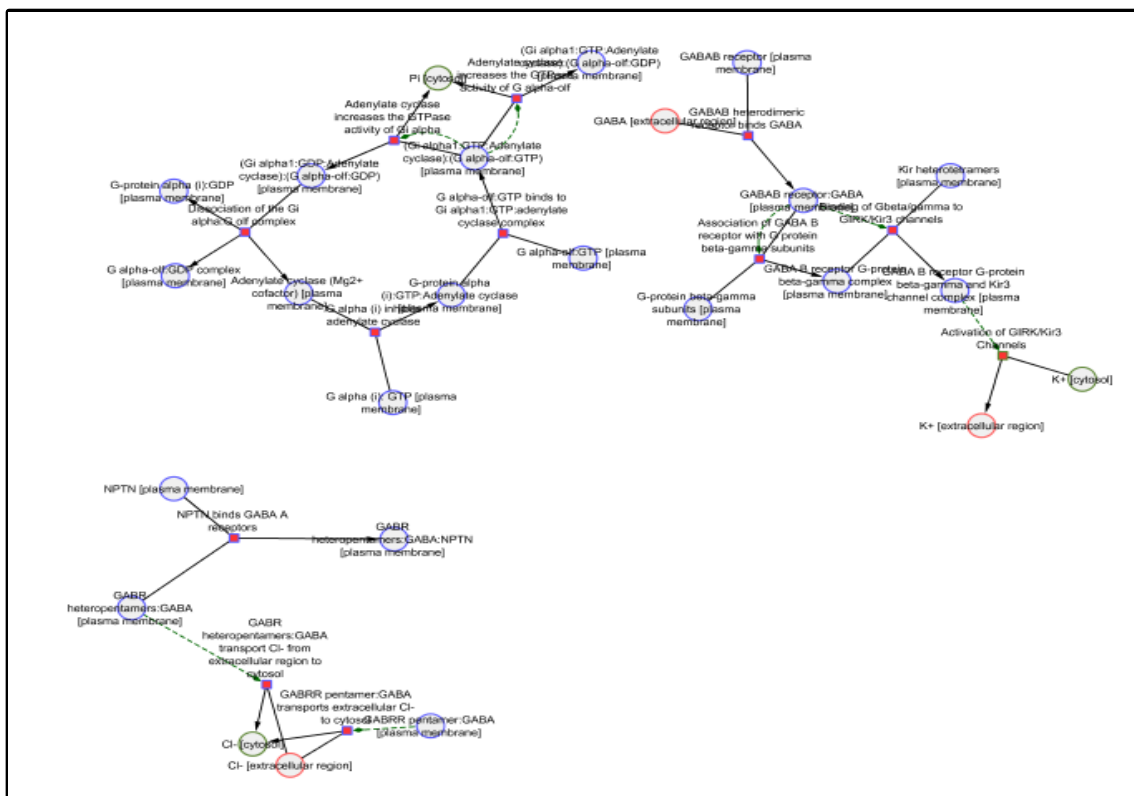


FIG 5.2(i)

The view in 3 different parts of a neuronal system.

The above figure gives the network in cytosol, extracellular region and plasma membrane. They are represented in the form of the green pentagons which shows the connection to other ions etc., the tiny coloured square are used as

binders. This shows the connection of the receptor in producing the products which leads us in finding strings of GABRB3.

STRING:

String is used to visualize a connection between the genes with the relatively functional protein inhibitors. 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. The latest version 10.5 contains information on about 9.6 million proteins from more than 2000 organisms.

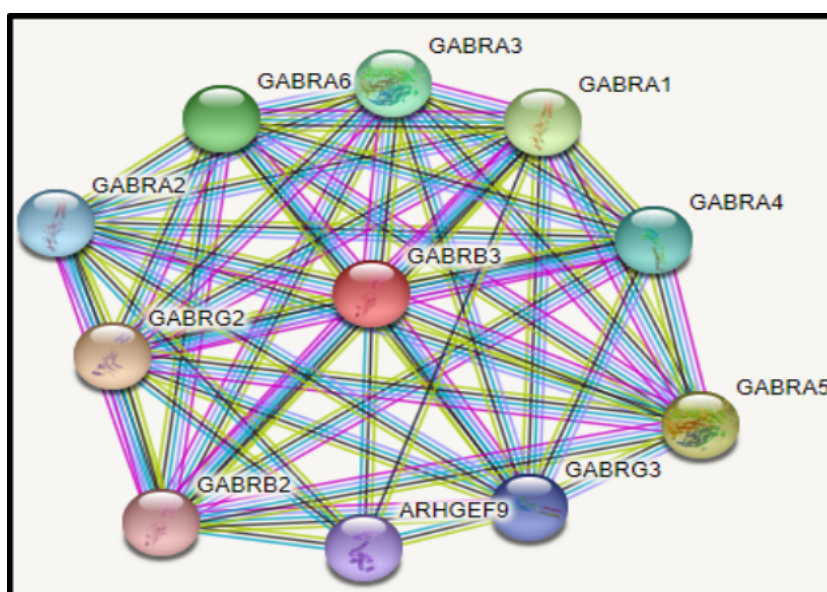


FIG 5.2(j)

The protein products of GABRB3.

These are the product of the genes i.e, proteins related to GABRB3.

They may be related directly or functionally related to this gene which shows the factorial changes that affect the human brain function and if there are any mutations then all these together show effect.

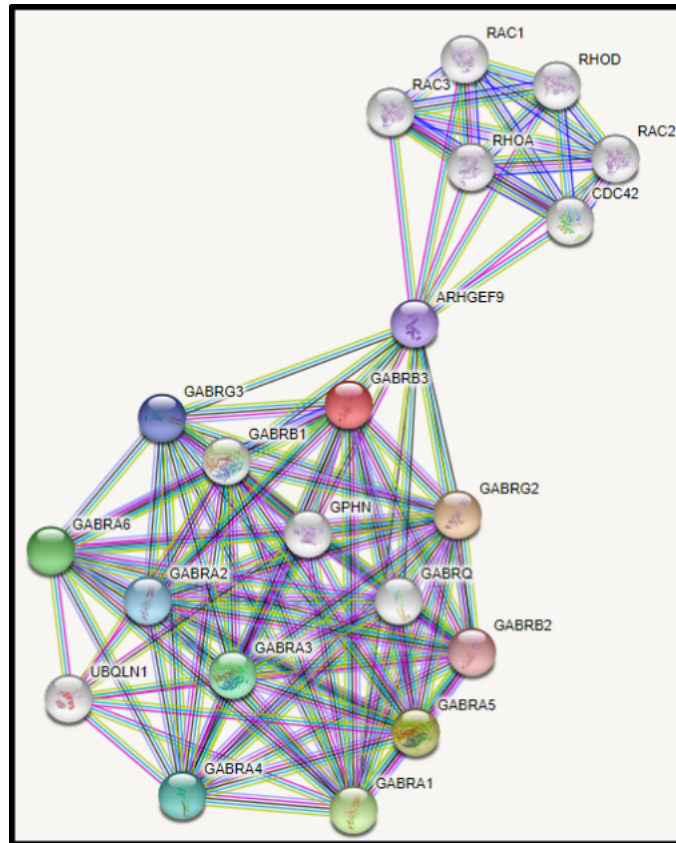


FIG 5.2(j)

The connection between the proteins .

In this ARHGEF9 is the binding between the other outer functionally related proteins which are the products of the different genes produced by chr15q11-chr15q13.

Thus it proves that it effects other gene products also.

SNP(single-nucleotide polymorphism):

To find the relativity we went a little further by trying to finding the SNP's for GABRB3

A single-nucleotide polymorphism (SNP) is a substitution of a single nucleotide that occurs at a specific position in the genome, where each variation is present at a level of 0.5% from person to person in the population. SNPs pinpoint differences in our susceptibility to a wide range of diseases (e.g. sickle-cell anemia, β -thalassemia and cystic fibrosis result from SNPs). The severity of illness and the way the body responds to treatments are also manifestations of genetic variations. For example, a single-base mutation in the APOE (apolipoprotein E) gene is associated with a lower risk for Alzheimer's disease.

Using this as an example we tried performong the SNP for GABRB3 as it is a rare single-based mutation for savant syndrome.

The dbSNP is the website database used to retrieve the SNP for GABRB3. The dbSNP has been designed to support submissions and research into a broad range of biological problems. These include physical mapping, functional analysis, pharmacogenomics, association studies, and evolutionary studies. Because dbSNP was developed to complement GenBank, it may contain nucleotide sequences from any organism.

rs20318		Current Build 153 Released July 9, 2019	
Organism	<i>Homo sapiens</i>	Clinical Significance	Reported in ClinVar
Position	chr15:26773650 (GRCh38.p12)	Gene : Consequence	GABRB3 : Synonymous Variant LOC112268151 : 2KB Upstream Variant
Alleles	G>A	Publications	2 citations LitVar3
Variation Type	SNV Single Nucleotide Variation	Genomic View	Sees on genome
Frequency	A=0.219899 (36319/165162, GnomAD_exome) A=0.154657 (19420/125568, TOPMED) A=0.14986 (4675/31196, GnomAD) (+ 8 more)		

Variant Details	Genomic Placements
Clinical Significance	Sequence name Change
Frequency	GABRB3 RefSeqGene NG_012836.1:g.5131C>T
Aliases	GRCh37.p13 chr 15 NC_000015.9:g.27018797G>A
Submissions	GRCh38.p12 chr 15 NC_000015.10:g.26773650G>A
History	
Publications	

Gene: GABRB3 , gamma-aminobutyric acid type A receptor beta3 subunit (minus strand)			
Molecule type	Change	Amino acid[Codon]	SO Term
GABRB3 transcript variant 1	NM_000814.6:c.	N/A	Genic Upstream Transcript Variant
GABRB3 transcript variant 2	NM_021912.5:c.75C>T	P [CCG] > P [CCT]	Coding Sequence Variant
GABRB3 transcript variant 3	NM_001191320.1:c.	N/A	Genic Upstream

FIG 5.2(k)

The SNP for GABRB3.

As the variant is a single mutation related there were only one snp for this syndrome there were snps of the other functionally related. The SNPs can be found from NCBI itself. All other SNPs were mentioned to be merged in to rs20318. Thus we were left with only this to collect the LD for GABRB3.

A single-nucleotide variant (SNV) is a variation in a single nucleotide without any limitations of frequency and may arise in somatic cells. A somatic single-nucleotide variation (e.g., caused by cancer) may also be called a single-nucleotide alteration.

LD (Linkage Disequilibrium):

Linkage disequilibrium is present when alleles from two nearby genetic variants commonly occur together in a non-random, linked fashion. Alleles of variants in linkage disequilibrium are correlated; with the degree of correlation generally greater in magnitude the closer the variants are in physical distance. Measures of linkage disequilibrium include D prime (D') and R squared (R²).

D prime (D') - an indicator of allelic segregation for two genetic variants. D' values range from 0 to 1 with higher values indicating tight linkage of alleles. A D' value of 0 indicates no linkage of alleles. A D' value of 1 indicates at least one expected haplotype combination is not observed.

R squared (R²) - a measure of correlation of alleles for two genetic variants.

R² values range from 0 to 1 with higher values indicating a higher degree of correlation. An R² value of 0 indicates alleles are independent, whereas an R² value of 1 indicates an allele of one variant perfectly predicts an allele of another variant.

R² is sensitive to allele frequency.

Goodness of Fit (X² and p-value) - statistical test testing whether observed haplotype counts follow frequencies expected from variant allele frequencies. High chi-square statistics and low p-values are evidence that haplotype counts deviate from expected values and suggest linkage disequilibrium may be present.

LDlink is the website used for the finding the LD for rs20318.

LDlink consists of nine modules:

LDassoc, LDhap, LDmatrix, LDpair, LDpop, LDproxy, LDtrait, SNPchip, and SNPclip. Each module can be accessed by clicking on the desired tab at the top of all LDlink pages.

LDhap - Calculate population-specific haplotype frequencies of all haplotypes observed for a list of query variants.

Input:

List of RS numbers - this can either be entered one per line in the text entry box or uploaded as a file that contains a list of RS numbers in the first column. A maximum of 30 variant RS numbers are permitted. All input variants must be on the same chromosome and match a bi-allelic variant. The text entry field is automatically filled with the contents of the uploaded file.

Reference population(s) - selected from the drop down menu. At least one 1000 Genomes Project sub-population is required, but more than one may be selected.

Output:

Table of observed haplotypes - haplotypes with frequencies greater than 1 percent are displayed vertically and ordered by observed frequency in the selected query sub-population. Variant genotypes are reported in rows and are sorted by genomic position. Queries should be limited to nearby variants, since haplotype

switch rate errors become more common as genomic distance increases. Links are available to dbSNP RS numbers and coordinates in the UCSC Genome Browser.

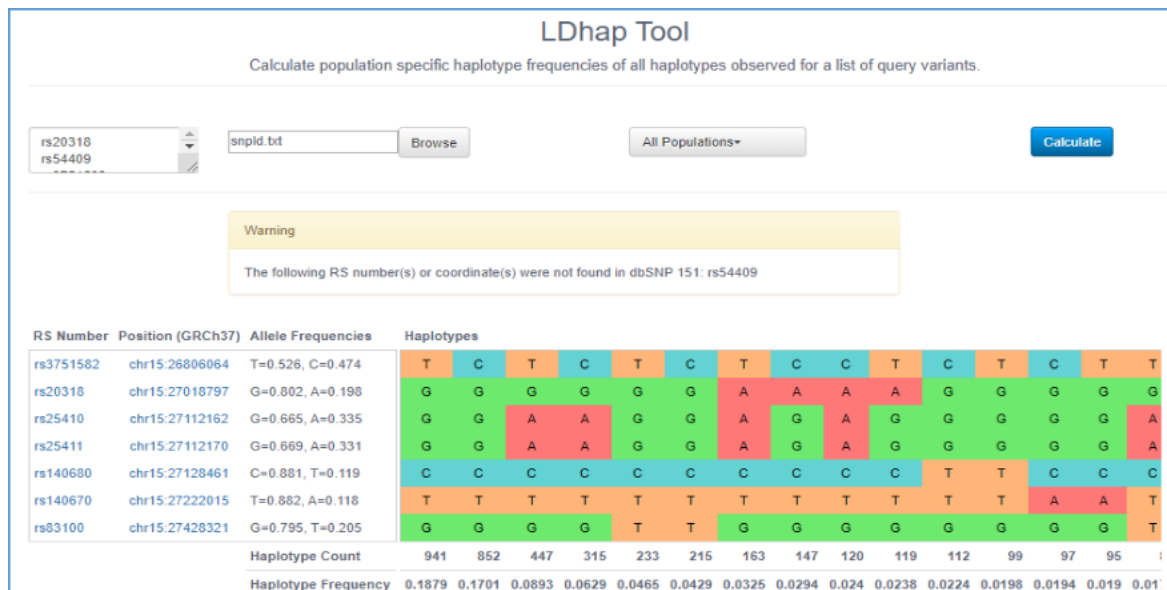


FIG 5.2(l)

LDhap for rs20318..

The haplotypes for the SNP are calculated among the selected population and the result are displayed.

LDmatrix - Create an interactive heatmap matrix of pairwise linkage disequilibrium statistics.

Input: List of RS numbers - this can either be entered one per line in the text entry box or uploaded as a file that contains a list of RS numbers in the first column. A maximum of 300 variant RS numbers are permitted. All input variants must be on the same chromosome and match a bi-allelic variant. The text entry field is automatically filled with the contents of the uploaded file.

Reference population(s) - selected from the drop down menu. At least one 1000 Genomes Project sub-population is required, but more than one may be selected.

As we are looking to form a matrix so we collected the SNP's for all the related functional protein and it has to be for the same gene/protein produced protein SNP's.

The snp retrieved are:

rs3751582,
rs20318,
rs25410,
rs25411,
rs140680,
rs140670.

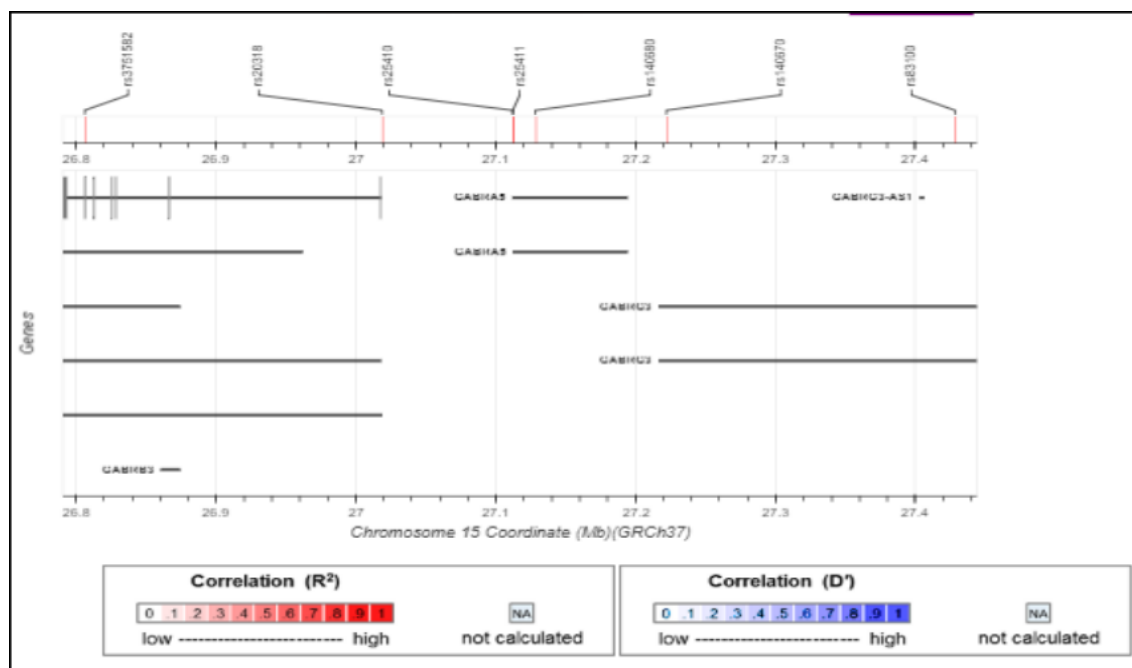
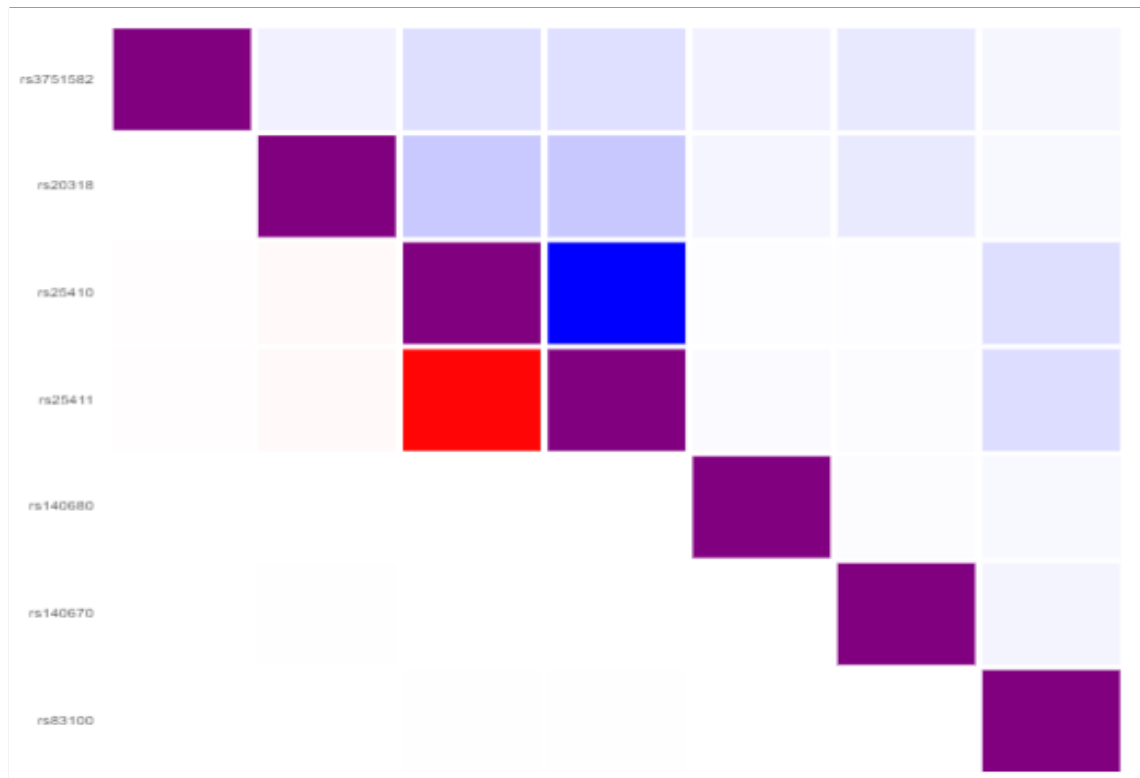


FIG 5.2(m)

LDmatrix for rs20318.

Output: Interactive heat map - a square plot with dimensions equal to the number of query variants that match a dbSNP RS number. Hovering over the plot with the mouse will display pairwise LD metrics for the respective row and column variants. Variants are ordered by genomic coordinates.

D prime download - download a file of all pairwise D' statistics.

R square download - download a file of all pairwise R2 statistics.

D depends on allele frequencies: Value can range from -0.25 to 0.25 Researchers suggested the value should be normalized.

- Based on the theoretical maximum and minimum relative to the value of D .
- When $D \geq 0$

$$D = \frac{D'}{D_{\max}}$$

$D_{\max}$ is the smaller of p_1q_2 and p_2q_1 .

- When $D < 0$ min

$$D = \frac{D'}{D_{\min}}$$

$D_{\min}$ is the larger of $-p_1q_1$ and $-p_2q_2$.

Another LD measure

- Correlation between a pair of loci is calculated using the following formula
- Value is r
- Or frequently r^2 .

$$r^2 = \frac{D^2}{p_1 p_2 q_1 q_2}$$

- Ranges from
- $r^2 = 0$
Loci are in complete linkage equilibrium

- $r^2 = 1$
Loci are in complete linkage disequilibrium

LDtrait -

Search if a list of variants (or variants in LD with those variants) that have previously been associated with a trait or disease. Trait and disease data is updated nightly from the GWAS Catalog. Problematic data entries in the GWAS Catalog can be browsed here.

Input:

List of RS numbers - this can either be entered one per line in the text entry box or uploaded as a file that contains a list of RS numbers in the first column. A maximum of 50 variant RS numbers or chromosomal coordinates (GRCh37) are permitted. All input variants must match a bi-allelic variant. The text entry field is automatically filled with the contents of the uploaded file.

Reference population(s) - selected from the drop down menu. At least one 1000 Genomes Project sub-population is required, but more than one may be selected.

R2/D' toggle - select if desired output is pruned from a threshold based on estimated R2 or D'.

R2/D' threshold - set threshold for LD pruning. Any variants within +/- of the specified genomic window and R2 or D' less than the threshold will be removed.

Value needs to be in the range 0 to 1. Default value is 0.1.

Window size - set genomic window size for LD pruning. Specify a value greater than or equal to zero and less than or equal to 1,000,000bp. Default value is +/- 500,000bp.

LDtrait Tool

Search if a list of variants (or variants in LD with those variants) have previously been associated with a trait or disease.

All Populations▼

Threshold
 D':

Warning

The following RS number(s) or coordinate(s) were not found in dbSNP 151: rs54409

Variants in LD with GWAS Catalog

Show entries

Search:

RS Number	GWAS Trait	RS Number	Position (GRCh37)	Alleles	R ²	D'	LDpair	Risk Allele Frequency	Beta or OR	Effect Size (95% CI)	P-value	GWAS Catalog
rs20318	Skin pigmentation	rs11858919	chr15:26599133	C=0.974, T=0.026	0.0065	1.0	link	NR	7.5900	4.35-10.83	1x10 ⁻⁸	link
rs3751582		rs149446621	chr15:26702986	C=0.998, T=0.002	0.0004	1.0	link	0.013	0.1542	0.087-0.221	1x10 ⁻¹	link
rs83100	Height	rs185226189	chr15:27030776	A=0.001, G=0.999	0.0002	1.0	link	NA	0.4411	0.25-0.64	3x10 ⁻¹	link
rs140670	Interleukin-4 levels	rs116046250	chr15:27231950	G=0.013, T=0.987	0.0033	1.0	link	0.046	2.9500	1.92-4.54	4x10 ⁻⁵	link

Showing 1 to 4 of 4 entries

FIG 5.2(n)

LDtrait Tool for rs20318.

Output:

Variants in LD with GWAS Catalog - a list of queried variants in LD with a variant reported in the GWAS Catalog. Each variant in the list is a clickable link that brings up a detailed table showing disease-associated variants that are in a +/- 500 KB window and in linkage disequilibrium with the variant.

Details Tables - output table that appears when a variant in the variant list is clicked. Details are provided on GWAS trait, genomic position, alleles, R2, D', Effect Size (95% CI), Beta or OR, and P-value. External links lead to the variant pair in LDpair and result variant in the GWAS Catalog.

Variants with Warnings - output table that appears when a variant produces a warning in LDtrait. Common reasons for a variant to be on the warning list are if the variant is not found in dbSNP or if no variants in LD are found within window of the GWAS Catalog. Details are provided on genomic position and why the variant was excluded from the variant list.

SNPclip - Prune a list of variants for linkage disequilibrium.

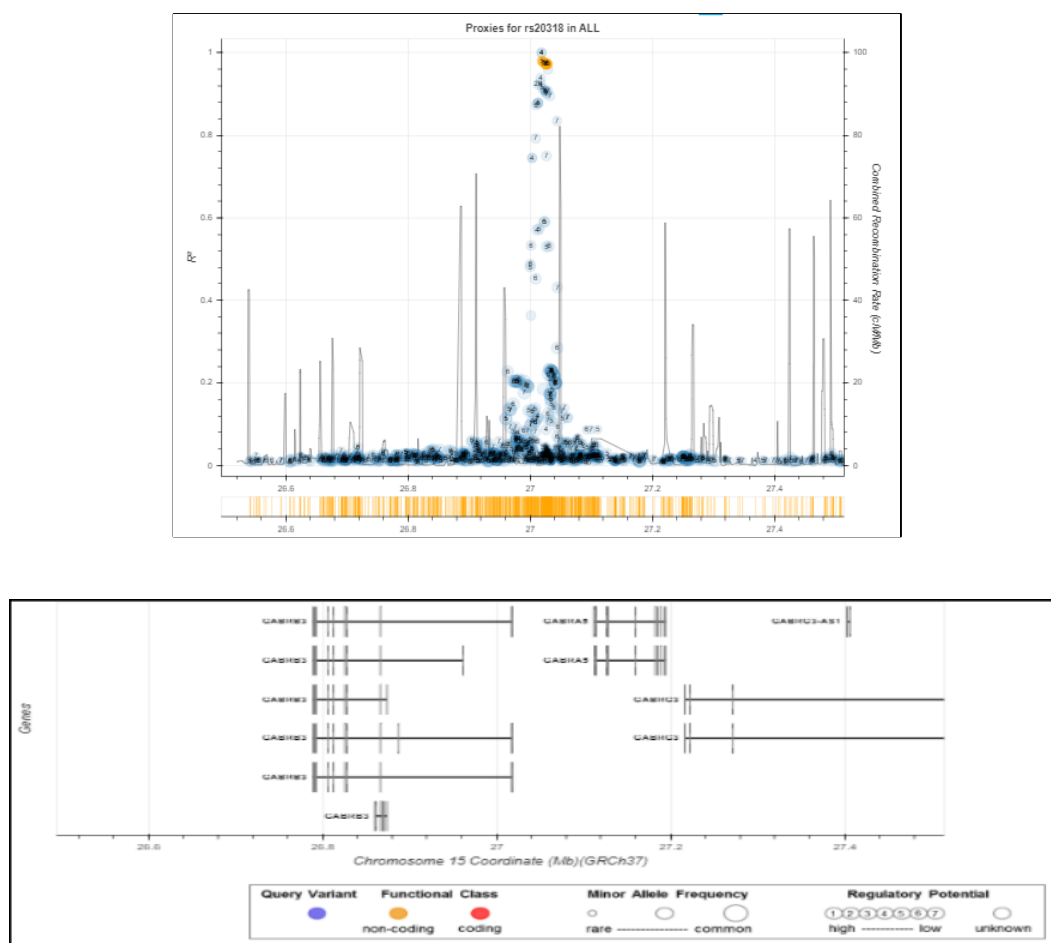
Input:

List of RS numbers - this can either be entered one per line in the text entry box or uploaded as a file that contains a list of RS numbers in the first column. A maximum of 5,000 variant RS numbers are permitted. All input variants must be on the same chromosome and match a bi-allelic variant. The text entry field is automatically filled with the contents of the uploaded file.

Reference population(s) - selected from the drop down menu. At least one 1000 Genomes Project sub-population is required, but more than one may be selected.

R2 threshold - set R2 threshold for LD pruning. One of each pair of variants with a R2 greater than the threshold is removed. Value needs to be in the range 0 to 1. Default value is 0.1.

MAF threshold - set MAF threshold for LD pruning. Variants with a MAF less than or equal to the threshold are removed. Value needs to be in the range 0 to 1. Default value is 0.01.



.FIG 5.2(o,p)

SNPclip Tool for rs20318.

Proxy Variants

Show entries

Search:

RS Number	Chr	Position (GRCh37)	Alleles	MAF	Distance	D'	R ²	Correlated Alleles	RegulomeDB	HaploReg	Functional Class
rs20317	15	27018937	(G/C)	0.1981	140	1.0	1.0	G=G,A=C	4		NA
rs4905902	15	27019768	(A/G)	0.1997	971	0.995	0.9801	G=A,A=G	5		NA
rs12439168	15	27022368	(T/C)	0.1993	3571	0.9924	0.9776	G=T,A=C	5		NA
rs61996891	15	27028597	(A/C)	0.2001	9800	0.9924	0.9727	G=A,A=C	6		NA
rs77189159	15	27026993	(C/T)	0.2001	8196	0.9924	0.9727	G=C,A=T	7		NA
rs80151887	15	27026954	(C/G)	0.2001	8157	0.9924	0.9727	G=C,A=G	7		NA
rs61996888	15	27026450	(A/G)	0.2001	7653	0.9924	0.9727	G=A,A=G	3b		NA
rs61996885	15	27025718	(T/C)	0.2001	6921	0.9924	0.9727	G=T,A=C	6		NA
rs148855686	15	27029582	(AATGT/-)	0.2019	10785	0.9912	0.9594	G=AATGT,A=-	.		NA
rs45488192	15	27017253	(G/T)	0.2071	1544	0.9962	0.9387	G=G,A=T	4		NA

Showing 1 to 10 of 1,198 entries

Download all proxy variants

Previous 2 3 4 5 ... 120 Next

FIG 5.2(q)

SNPclip Tool for rs20318.

Output:

LD Thinned Variant List - a list of LD pruned variants based on the specified SNPclip parameters. Each variant in the list is a clickable link that brings up a detailed table showing other variants that are in linkage disequilibrium with the variant. Variants are ordered by input order, so to force a variant to be in the LD thinned list it should be at the top of the input list.

Details Tables - output table that appears when a variant in the thinned variant list is clicked. Details are provided on genomic position, alleles, and why the variant was included or excluded from the thinned variant list. External links lead to the variant RS number in dbSNP and coordinates in the UCSC Genome Browser.

Variants with Warnings - output table that appears when a variant produces a warning in SNPclip. Common reasons for a variant to be on the warning list include a variant with an MAF below the MAF threshold, a query that is not a RS number, and a RS number not found in the 1000G reference VCF file. Details are provided on genomic position, alleles, and why the variant was included or excluded from the thinned variant list. External links lead to the variant RS number in dbSNP and coordinates in the UCSC Genome Browser.

The current study confirms the role of GABRB3 as an important candidate gene in both ASD and Savant syndrome.

CHAPTER -6

CONCLUSION

The savant syndrome is a unique yet a very problematic disorder. Our main goal was to analyze the gene related interpret a pathway and form a network. But we went a head and tried finding the relatively functional proteins and checked for the evidence to prove that this specific gene effects the other chromosomal gene products and retrieved the SNP's needed. Later we checked for LD's for the population survey for some may thousands of them and found that the GABRB3 is strong candidate that effects many other genes and is a cause for many more related disorders. This document is a combination of all the experience we have along the journey of learning about the syndrome along with the kids and the beauty of their innocence that the society has marked as mentally challenged but who are extraordinary talented if taken a better care of. We hope this report could at-least change the views of some readers about these extraordinarily gorgeous and blessed people and hope they are treated as common and normal civilians at the most.

