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LIST OF ABBREVIATIONS

ATP	Adenosine triphosphate
ATS	Andersen Tawil Syndrome
BFNS	Benign familial neonatal seizures
CIP	Congenital in-sensitivity to pain
DBMS	Database management system
FHM	Familial hemiplegic migraine
FHM1	Familial hemiplegic migraine type-1
GYG	Glycine tyrosine glycine
Hypo PP	Hypokalemic periodic paralysis
IDE	Integrated development environment
MS SQL	Microsoft Structured query language
MSD	Membrane spanning domain
NBD	Nucleotide binding domain
NCKB	Neurological Channelopathic Knowledge Base
PAM	Potassium-aggravated myotonia
PD	Paroxysmal dyskinesias
PEM	Primary erythro-melalgia
PEPD	Paroxysmal extreme pain disorder
PMC	Para-myotonia congenita
S1-S6	Segment 1- Segment 6
SQL	Structured query language
TM	Transmembrane domain

Neurological Channelopathic Knowledge Base (NCKB): An application software for Ion channels and Neurological channelopathies

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ABSTRACT

Biological databases are the central repositories where important experimental information is stored. Raw data is useless until or unless it is backed up by a good database management system. RDBMS has the capability of deriving implicit meaning out of raw facts. In modern biology, databases turned their faces towards the development in the field of bioinformatics. Now a day databases are being lodged with the data analysis tool where that data be a DNA sequence, protein sequence or protein structure. Data is meaningless with the absence of its analytic tools in bioinformatics. Structured query language is a potent non procedural language which is very well being used for the database creation. Such a platform is provided by Microsoft in form of MS SQL Server. Moreover interactive user interface is also an interesting criterion for the database development. Today database have spread their arms in every field of biology. Till date in field of neuroscience various databases are accessible which is having information regarding gene expression, neurons, macroscopic brain structure, and neurological or psychiatric disorders. But still there is no database repository for neurological channelopathies. Neurological Channelopathic Knowledge Base (NCKB) will provide detailed pathological information about the neurological channelopathies as well as detailed information about the ion channels involved in the neurological disorders. This database has been integrated with online bioinformatical tools.

Herein we have developed i) Neurological Channelopathic Knowledge Base- a software with complete package of Neurological channelopedia, Neurological channelopathies database and interactive data retrieval user interface.

INTRODUCTION

Neurological channelopathic knowledge base (NCKB) software is an appeal for data warehousing of neurological disorders related with the dysfunctional ion channels. Databases are the organized collection of relevant data which provide assistance to the scientists for leading the research in their respective area. These databases now a day fledged by the analytical tools for the interpretation of biological data. Due to which bioinformatics came into picture to assist in storing, extracting, organizing and analysing the valuable information out of the raw sequence and structural data. These databases can be classified into three categories based on the method of procured information namely Primary, Secondary and Composite database. This database serves as a composite database. The database designing concept is explained in **Figure 1.**

Biological databases execute two fundamental functions: -

1. **Accessibility of biological data to the researchers.**
   Information about a particular field and use of that information can be explored by the scientists to extend their research from the present state. This enables in the advancement of biological research.
2. **Availability of biological data in computer readable form.**
   For the analysis of biological information it is necessary to have it in computer readable form such that computational tools can be applied on them.

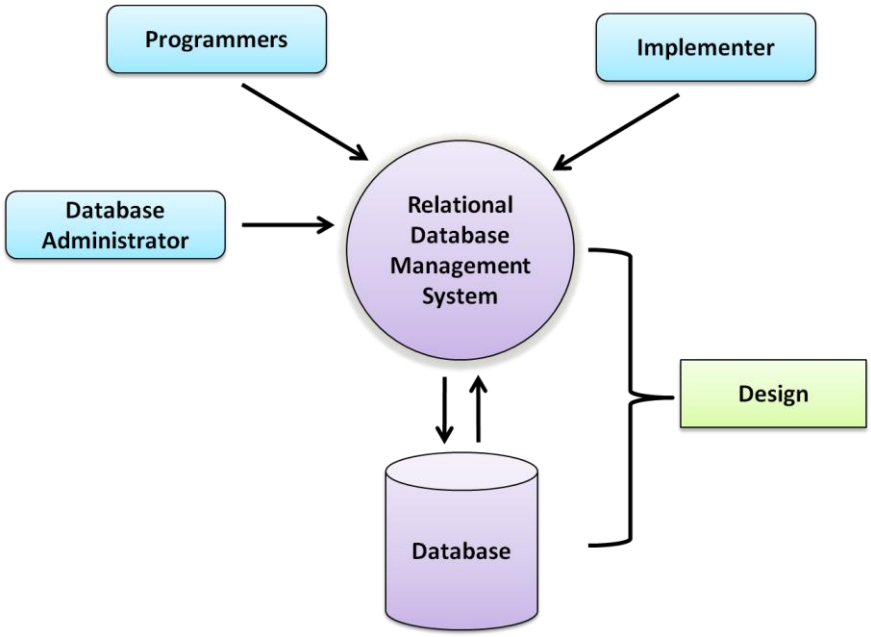


Figure 1: Database design concept

For the access of a database, Database Management System (DBMS) is the essential requirement. It plays a crucial role in application development that can interact with the user, other applications and the database itself to capture and analyse data. SQL is a standard language for accessing databases.

Database Management system: -

It is a collection of interrelated data and set of programs to access those data. Its primary use is to provide a way to store and retrieve data base information i.e. both conveniently and efficiently. Architecture for a DBMS is illustrated in **Figure 2.**

DBMS is a general purpose software system that facilitates four purposes: -

1) **Defining: -** it involves specifying data types, structures and constraints for the data to be stored in database.
2) **Constructing**: - it involves storing the data on some storage medium i.e. controlled by DBMS.
3) **Manipulating**: - it includes such functions as querying the database to retrieve specific data, update the data to reflect the changes and generate reports from the data.
4) **Sharing: -** it allows multiple users & programs to access database concurrently.

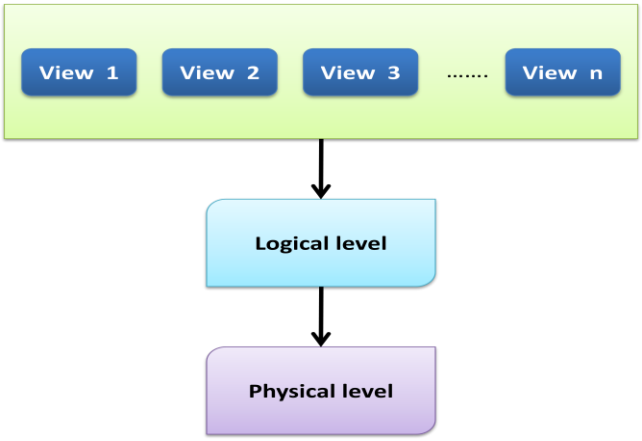


Figure 2: Architecture for a database system

Neurological Channelopathic Knowledge Base (NCKB) has been designed with the help of Microsoft SQL server program whereas its software package has been designed with help of Microsoft Visual Studio program. It is user friendly and provides access to the online available bioinformatics analytical tools. SQL and C-sharp (C#) languages has been used for its development. It has been designed with the help of two software that involves 'SQL Server Management Studio 2005' and 'Microsoft Visual Studio 2008'. NCKB contains two databases that are Neurological Channelopedia and Neurological Channelopathies. Neurological Channelopedia possess information about the ion channels while Neurological channelopathic database stores the genetic, structural and mechanistic information about the channelopathies. This software has been backed with exceptional security that underlies at three levels. One at NCKB software installation in form of a 'Product Key', another at software access in form of 'Login Password' and finally at the database installation in the form of 'SQL connection password'. Moreover exceptions have been handled with care that identified the absolute errors involved.

MS SQL is a relational database management system whose primary function is to store and retrieve data on requisition by other software applications. Structural query language is a programming language based on relational algebra and relational tuple calculus for coping data in a relational database management system. The horizon of SQL comprises data

insertion, querying, updating, deletion, schema creation and mitigation, and data access control.

Microsoft Visual Studio is a program that contains the development tools for creating various web, desktop and mobile applications. It has an integrated development environment (IDE) that allows sharing of tools and creation of mixed-language solutions. A conceptual model of data retrieval is designed in **Figure 3.**

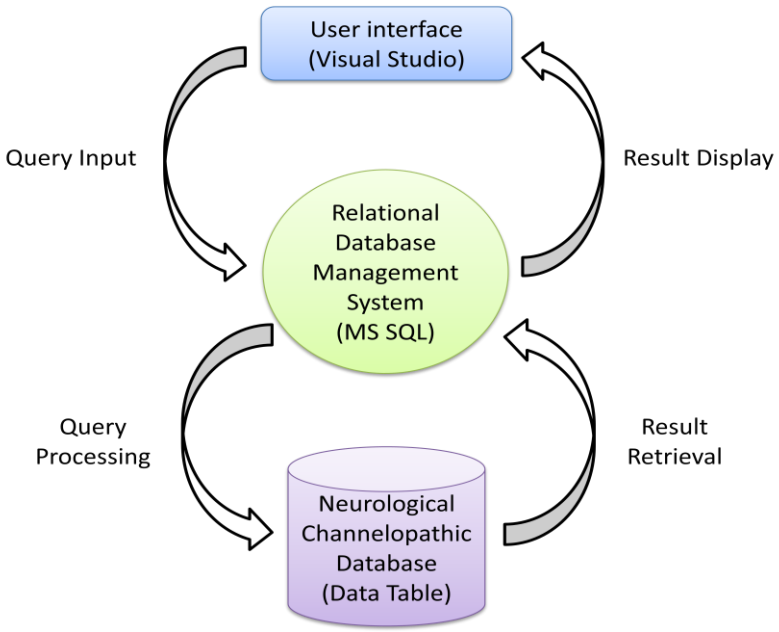


Figure 3: A conceptual model of information retrieval

Neurological Channelopathic Knowledge Base contains two databases: -

1. **Neurological Channelopedia**
   It contains the relevant information about all the ion channels which is involved in the neurological disease.

   Schema of Neurological channelopedia: -

Channel Name	Subtype	Gene encoding subtypes	Tissue specificity	Subcellular location	Structure	Physiological role	Involvement in disease	References

2. **Neurological Channelopathies**
   It contains the relevant information about the neurological channelopathies.

   Schema of Neurological channelopathies: -

Tissue affected	Ion channels	Gene	Channel subunit	Disease caused	Symptoms	Mechanism	References

Neurological channelopathic database covers broad informational aspects of neurological disorders associated with ion channel dysfunctions.

REVIEW OF LITERATURE

Normal functioning of neurological tissues lies in the intricate interplay among ion channels which is responsible for the membrane excitability. Nonfunctional ion channels are accountable for special class of neurological disorders termed as neurological channelopathies. "Neurological channelopathies" is attributed to the neurological disorders which are provoked due to genetic aberration (mutation) in the ion channels (Kullmann and Hanna., 2002). However, its phenotype is covering extensive areas ranging from epilepsies, migraine, and periodic paralysis to pain disorders. Eminent candidates that are responsible for aiding transient neurological disorders is found to be stress, caffeine and ethanol (Raike *et al.*, 2013).

Genetic neurological channelopathies possesses three typical hallmarks, for instance: -

- Paroxysmal in nature: It means impaired neurological functional episodes separated by periods of normality are experienced by the patient. Some of these examples include migraine and epilepsy (Kullmann and Hanna., 2002; Graves and Hanna., 2005; Kullmann and Waxman., 2010).
- Environmental onset: Episodes are set off by environmental factors like thermal, physical and emotional stresses.
- Genetic neurological channelopathy is prone to natural antiquity: Frequency of attack conventionally dwindles with the time but the patient faces some neurological disability.

Clinical phenotypes include muscle disorders such as periodic paralysis and myotonia (muscle stiffness), disorders of peripheral nerve excitability such as neuromyotonia and brain disorders like migraine and epilepsy (Graves and Hanna., 2005).

3.1 Importance of Ion Channels

In an organism, ion channels play an important role for the regulation of cellular homoeostasis. The ion channels are the molecular basis of membrane excitability (synaptic transmission, action potentials, sensory transduction; Pak and Pinto, 1976) that has been established for the past five decades but molecular entities are characterized only a decade back. Any alteration or malfunctioning in ion channels is incompatible with life (Graves and Hanna, 2005). Ion channels are present in the plasma membrane of the cells, organelles and monitored a critical role in cardiac, nervous, and immune systems. Several studies proved that ion channels are important target of many clinically used drugs, for instance amitriptyline targets Na_v1 channels and ziconotide targets $Ca_v2.2$ channel (Kaczorowski *et al.*, 2008).

3.2 Ion Channels and Underlying Genetic Diversity

3.2.1 Sodium Ion Channel

Sodium channel allows the inflow of Na^+ ions once excited due to potential difference across the plasma membrane of the cell. Further, depolarization activates the sodium channel which provides a passage of sodium ion into the muscle fiber or neuron, thereby forming the depolarization upstroke of the action potential. With the opening

of sodium channel, membrane potential shifted from -70mV to less negative values due to the influx of positive sodium ions thereby elevating the positive charge inside the membrane. Kariev and Green proposed and provided the evidence that protons constitute the gating current to open the channel (Kariev and Green, 2012). Based on the genetic diversity they are classified into different subtypes (i.e. $Na_v1.1$ to $Na_v1.9$) that are known to be associated with various diseases summarized in **Table 1.**

Channel Name	Subtypes	Genes encoding subtypes	Tissue Specificity	Subcellular location	Subunit structure	Physiological Role	Involvement in disease	References
Sodium (Na_V) Channel	Na_V 1.1	SCN1A	Adult brain, especially in Purkinje cells	Cell bodies	Na_v type-1 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Control of action potential generation and propagation	Myoclonic epilepsy	(Kalume *et al.*, 2007) (Spampanato *et al.*, 2003)
	Na_V 1.2	SCN2A	Central neurons, peripheral neurons	Axon initial segment of Cerebellar granule cells	Na_v type-2 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Control of action potential generation and propagation	Inherited febrile seizures	**(**Kearney *et al.*, 2001) (Shi *et al.*, 2012)
	Na_V 1.3	SCN3A	Developing CNS, peripheral neurons and cardiac myocytes	Membrane	Na_v type-3 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Fast activation and Inactivation Kinetics	Hyper excitability in epileptic patient	(Estacion *et al.*,2010)
	Na_V 1.4	SCN4A	Skeletal muscle	Membrane	Na_v type-4 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Generation and propagation of action potentials that initiate muscle contraction	Several myotonia and periodic paralysis disorders, Arrhythmias	(Anyukhovsky *et al.*, 2011)
	Na_V 1.5	SCN5A	Brain, cardiac muscle	Axon, Co-localized with Neurofilaments	Na_v type-5 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Action potential generation & propagation in cardiac tissue and brain	Syncope, Seizures, Cardiac arrhythmias Long QT syndrome (LQTS), Brugada syndrome, Cardiac conduction disease	(Hu *et al.*, 2010) (Tan *et al.*, 2007)
	Na_V 1.6	SCN8A	Cerebellar granule cells	Mature nodes along compact myelinated axons, dendrites	Na_v type-8 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Most prominently expressed and potential generation in various types of tissues	Cognitive impairment with or without cerebellar ataxia (CIAT), Epileptic encephalopathy, early infantile, type 13 (EIEE13)	(Trudeau *et al.*, 2006) (Osorio *et al.*, 2005)
	Na_v 1.7	SCN9A	Nociceptors (Nerves transmitting pain signals)	Membrane	Na_v type-9 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Responsible for carrying pain signals to brain	Erythromelalgia, Paroxysmal extreme pain disorder, Congenital insensitivity to pain(CIP)	(Cregg *et al.*, 2013) (Estacion *et al.*, 2011) (Klein *et al.*, 2013)
	Na_v 1.8	SCN10A	Peripheral sensory nervous system	Membrane	Na_v type-10 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Transmits pain signals to CNS in cold temperature	Pain and Paresthesias	(Faber *et al.*, 2012)
	Na_v 1.9	SCN11A	Heart and Dorsal root ganglion neurons	Trigeminal neurones and their axons	Na_v type-11 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Involved in pain related signaling	Mechanical and Heat pain hypersensitivity	(Lolignier *et al.*, 2011)
	Na_V β1	SCN1B	Muscle and Neuronal cells	Membrane	Na_v type-1 β-subunit. Single domain. Auxiliary subunit	Modulate channel gating kinetics	Brugada syndrome, Generalized epilepsy with febrile seizures plus type 1	(Audenaert *et al.*, 2003) (Patino *et al.*, 2011)
	Na_V β2	SCN2B	White matter tracts in the cerebellum, Hippocampal, cortical pyramidal neurons, and cerebellar purkinje neurons	At the membrane of Cell bodies and Nodes of Ranvier	Na_v type-2 β-subunit. Single domain. Auxiliary subunit	Modulate channel gating kinetics	Brugada Syndrome	(Riuro *et al.*, 2013)
	Na_V β3	SCN3B	Contractile myocardium	Membrane	Na_v type-3 β-subunit. Single domain. Auxiliary subunit	Modulate channel gating kinetics	Brugada syndrome type 7	(Hu *et al.*, 2009) (Carmen *et al.*, 2010)
	Na_V β4	SCN4B	Dorsal root ganglia	Membrane	Na_v type-4 β-subunit. Single domain. Auxiliary subunit	Modulate channel gating kinetics	Long QT-syndrome type 10	(Medeiros-Domingo *et al.*, 2007)

Table 1: Sodium ion channel subtypes in association with various diseases

3.2.2 Potassium Ion Channel

Potassium channel is responsible for conducting K^+ ions level down the electrochemical gradient and involved in various functions for instance, excitation of neuronal cells, regulation of cell volume and secretion of hormones (Armstrong and Hille, 1998). With the opening of potassium channel in response to membrane depolarization, membrane potential drops down from +30mV to -70mV due to the efflux of positive ion, making more negative inside the membrane and therefore proceed towards repolarization of the membrane. Different family of potassium channels exist depending upon the method of gate opening that are ligand-gated potassium channel which requires binding of an ion, organic molecule and another one is voltage gated that require voltage stimulus for pore opening (MacKinnon, R. 2003). Mutations in these diverse potassium channel subtypes have been associated with diseases are elaborated in **Table 2.**

Channel Name	Subtypes	Genes encoding subtypes	Tissue Specificity	Sub cellular location	Structure	Physiological Role	Involvement in disease	References
Potassium (Kv) Channel	$K_v1.1$	KCNA1	Unmyelinated Axons, Cell Somas, Axon Terminals, Dendrites	Membrane, Transmembrane	K_v shaker member 1, α-subunit consist of six helical segments (S1-S6)	Circadian Rhythms, Neuronal Firing	Episodic Ataxia Type 1, Myokymia, Periodic Ataxia	(Orazio *et al.*, 2012) (Brew *et al.*, 2003) (Shook *et al.*, 2008)
	$K_v1.2$	KCNA2	Hippocampal Neuron Neocortex, Main olfactory bulb (MOB) and Cerebellum	Membrane, Multi-pass membrane protein	K_v shaker member 2, α-subunit consist of six helical segments (S1-S6)	Regulation of state Transitions and Repetitive activity in Striatal Medium Spiny Neurons	Cerebellar Ataxia, myokymia and neuromyotonia	(Pruss *et al.*, 2009) (Lorincz and Nusser., 2008)
	$K_v1.3$	KCNA3	Effector memory T-cells	Membrane, Multi-pass membrane protein	K_v shaker member 3, α-subunit consist of six helical segments (S1-S6)	Regulate several physiological functions of Lymphocytes, Cell Proliferation	Down syndrome Neural Progenitors	(Wulff *et al.*, 2003) (Cidad *et al.*, 2012)
	$K_v1.4$	KCNA4	Heart, Cerebellum	Membrane, Multi-pass membrane protein	K_v shaker member 4, α-subunit consist of six helical segments (S1-S6)	Modulating Electrophysiological Behavior	Chronic Pancreatitis, Hyperalgesia	(Chandy *et al.*, 2004) (Freedman *et al.*, 1992) (Leonard *et al.*, 1992)
	$K_v1.5$	KCNA5	Heart, Brain	Cell membrane, Multi-pass membrane protein	K_v shaker member 5, α-subunit consist of six helical segments (S1-S6)	Physiological processes in Brain and Muscle	Ischemia Affects	(Fedida *et al.*, 2003) (Gobrit *et al.*, 2007) (Vicente *et al.*, 2006) (Archer *et al.*, 2001) (Stapels *et al.*, 2010)
	$K_v1.6$	KCNA6	Ganglion Cell	Membrane, Multi-pass membrane protein	K_v shaker member 6, α-subunit consist of six helical segments (S1-S6)	Mediates the voltage-dependent potassium ion permeability of excitable membranes	Myokymia and Neuromyotonia	(van Poucke *et al.*, 2012)
	$K_v1.7$	KCNA7	Heart, Kidney, Skeletal Muscle	Membrane, Multi-pass membrane protein	K_v shaker member 7, α-subunit consist of six helical segments (S1-S6)	Important Role in the Repolarization of Cell Membranes	Acute myeloid Leukemia	(Finol-Urdaneta *et al.*, 2006) (Kashuba *et al.*, 2001)
	$K_v2.1$	KCNB1	CNS	Pyramidal Neurons in Cortex	K_v shab member 1, α-subunit consist of six helical segments (S1-S6)	Regulates Neuronal Excitability, Action Potential Duration and Tonic Spiking	Hyperalgesia	(Misonou *et al.*, 2005)
	$K_v2.2$	KCNB2	Trapezoid body neurons	Trapezoid body neurons	K_v shab member 2, α-subunit consist of six helical segments (S1-S6)	Regulate Action Potential Firing	Cardiovascular disease risk	(Johnston *et al.*, 2008) (Kihira *et al.*, 2010)
	$K_v3.1$	KCNC1	Cortex, Cerebellum, Hippocampus Neurons in the Globus Pallidus, CNS	Hippocampus Neurons in the Globus Pallidus	K_v shaw member 1, α-subunit consist of six helical segments (S1-S6)	Involved in Motor Control	Ataxia with prominent Hypermetria, Constitutive Hyperactivity, Sleep Loss, Impaired Motor performance, Tremor and Myoclonus	(Lewis *et al.*, 2004) (Espinosa *et al.*, 2008)
	$K_v3.2$	KCNC2	Cortical GABAergic Interneurons, Hippocampus Somatic, Proximal Dendritic Membrane Axons	Proximal Dendritic Membrane Axons, Cortical GABAergic Interneurons	K_v shaw member 2, Homo- or hetero tetramer, α-subunit consist of six helical segments (S1-S6)	Neurodevelopmental delay Cerebellar Ataxia	Susceptibility to Seizures	(Chow *et al.*, 1999) (Lau *et.al.*, 2000)

$K_v3.3$	KCNC3	Cortex, Basal Ganglia and Cerebellum	Membrane, Multi-pass membrane protein	K_v shaw member 3, Homo- or, α-subunit consist of six helical segments (S1-S6)	Involved in Motor Control	Constitutive Hyperactivity, Sleep Loss, Impaired Motor Performance, Ataxia, Tremor and Myoclonus	(Espinosa *et al.*, 2008)
$K_v4.1$	KCND1	Epithelial Cells, Alveolar and Mammary Epithelial Cells, Adipose Tissue-Derived Stem Cells	Multi-pass membrane protein, Alveolar Mammary Epithelial Cells Adipose Tissue-Derived Stem Cells	K_v shal member 1, Homo tetramer, α-subunit consist of six helical segments (S1-S6)	Contribute to cell Migration and Wound Healing	Gastric Cancer NOS, Malignant Neoplasm of Breast	(Sandhiya and Dkhar**.**, 2009)
$K_v4.2$	KCND2	Brain	Localized in the Dendrites near Postsynaptic Regions	K_v shal member 2,, α-subunit consist of six helical segments (S1-S6)	Regulate Synaptic Plasticity	Cardiovascular disease	(Jo *et al.*, 2010)
$K_v4.3$	KCND3	Rat Adult Brain and Heart Tissues	Molecular layer Interneurons	K_v shal member 3,, α-subunit consist of six helical segments (S1-S6)	Internalized in response to Glutamatergic stimulation in Purkinje Cells, Neuronal Somato-dendritic Interactions	Spin cerebellar Ataxia Type 1, Cerebellar Ataxia	(Hourez *et al.*, 2011)
$K_v7.2$	KCNQ2	Peripheral Nerve System	Membrane, Multi-pass membrane protein	K_v KQT like Subfamily member 2, Heteromultimer, α-subunit consist of six helical segments (S1-S6)	Regulate Neurotransmitter Release, Heart Rate, Insulin Secretion Neuronal Excitability, Epithelial electrolyte Transport, Smooth Muscle contraction	Myokymia and Neuromyotonia	(van Poucke *et al.*, 2012)
$K_v7.3$	KCNQ3	Distributed Broadly in Brain	Membrane, Multi-pass membrane protein	K_v KQT like Subfamily member 3, Heteromultimer, α-subunit consist of six helical segments (S1-S6)	Electrical Hyper excitability in BFNC	Familial Neonatal Convulsions (BFNC), Autosomal Dominant Epilepsy of Infancy, Myokymia	(Schroeder *et al.*, 1998) (Chung *et al.*, 2006)
$K_v7.4$	KCNQ4	Almost All Brain Regions	Discrete Nuclei Of Brainstem, Including the Mid- Brain	K_v KQT like Subfamily member 4, Homo/Hetero tetramer, α-subunit consist of six helical segments (S1-S6)	Participate in both pre- and Postsynaptic Modulation of basal and stimulated excitatory Neurotransmission	Chinese Non-Syndromic Hearing Loss Pedigree	(Kharkovets *et al.*, 2000)
$K_v7.5$	KCNQ5	Neocortex and the Hippocampal	Apical and Lateral Membranes	K_v KQT like Subfamily member 5, Heteromultimer , α-subunit consist of six helical segments (S1-S6)	Controlling Basal Anion Secretion	Epilepsy	(Yus-Najera *et al.*, 2003)

Table 2: Potassium ion channel subtypes in association with various diseases

3.2.3 Calcium Ion Channel

Calcium channels are responsible for mediating the flow of Ca^{2+} ions in response to either voltage or ligand and therefore designated as voltage gated or ligand gated calcium channel (Striggow and Ehrlich., 1996). Voltage gated calcium channel mediates the influx of Ca^{2+} ions along the electrochemical gradient across the plasma membrane and have been classified into transient (T-type), long-lasting (L-type) currents, N-, P/Q and R type according to their inactivation properties (Tsien *et al.*,1987; Llinas *et al.*,1992). These diverse channel subtypes associated with diseases have been summarized in **Table 3.** These calcium channels have been involved in a variety of functions that are triggering gene expression (Morgan and Curran., 1989), link membrane depolarization to intracellular signaling (Westenbroek *et al.*,1990), excitation-contraction coupling, rhythmic activity and excitation-secretion coupling (Bergsman *et al.*, 2000).

Channel Name	Subtypes	Genes encoding subtypes	Tissue Specificity	Sub cellular location	Subunit Structure	Physiological Role	Involvement in disease	References
Calcium (Ca_V) Channel	$Ca_V1.1$	CACNA1S	Skeletal Muscle	Located in Muscle Cells triad junctions	Ca_v L-type, α-1S subunit, Each α_1 subunit consists of 6 helical transmembrane segments (S1-S6)	Functions as a Voltage Sensor in Skeletal Muscle Excitation-Contraction Coupling	Hypokalemic Periodic Paralysis, Thyrotoxic Periodic paralysis and Malignant Hyperthermia Susceptibility	(Kung *et al.*, 2004) (Kim *et al.*, 2001)
	$Ca_V1.2$	CACNA1C	Brain, Heart, Ovary Neurons	Membrane; Multi-pass membrane protein	Ca_v L-type, α-1C subunit, Each α_1 subunit consists of 6 helical transmembrane segments (S1-S6)	Release of Hormones and Neurotransmitters	Vision, Hearing, and Gene Expression	(Kameda *et al.*, 2006) (Reuter H. 1983)
	$Ca_V1.3$	CACNA1D	Auditory Brainstem, Center Auditory Sensory hair Cells, Neuronal Cells and Some Epithelial Cells	Somato-dendritic Compartment of many Types of Neurones	Ca_v L-type, α-1D subunit, Each α_1 subunit consists of 6 helical transmembrane segments (S1-S6)	Regulate Intracellular Processes such as Contraction, Secretion, Neurotransmission and Gene Expression	Deafness	(Roberts *et al.*, 1990) (Satheesh *et al.*, 2012)
	$Ca_V1.4$	CACNA1F	Retina	Expressed in the Retina and Localizes at Ribbon Synapses in Cone and Rod photoreceptors	Ca_v L-type, α-1F subunit, Each α_1 subunit consists of 6 helical transmembrane segments (S1-S6)	Synaptic Transmission and Cellular organization in Retina	Congenital Stationary Night Blindness , Syndromic Autism, Schizophrenia	(McRory *et al.*, 2004) (Klassen *et al.*, 2011) (Wei and Hemmings., 2006)
	$Ca_V2.1$ (P/Q)	CACNA1A	Presynaptic Terminals Cerebellar Purkinje Cells Granule Cells, Cortex	Somato-Dendritic membranes throughout the brain	Ca_v P/Q-type, α-1A subunit, Each α_1 subunit consists of 6 helical transmembrane segments (S1-S6)	Mediating Neurotransmitter release in the Nervous System, Postsynaptic Integration, Neuroplasticity, Neural Excitability, and Gene Transcription	Spin cerebellar Ataxia Type 6	(Llinas *et al.*, 1992) (Mintz *et al.*, 1992) (Chen and Piedras-Rentería., 2007)
	$Ca_V2.2$ (N)	CACNA1B	Neuron, Retinal Ganglion cell	Multi-pass membrane protein	Ca_v N-type, α-1B subunit, Each α_1 subunit consists of 6 helical transmembrane segments (S1-S6)	Controls Neurotransmitter Release from Neurons	Episodic Ataxia Type 2, Schizophrenia and Bipolar Disorder	(Yasuda *et al.*, 2004) (Zhang *et al.*, 2008)
	Ca_v 2.3 (R)	CACNA1E	Neuronal Tissues (Kidney)	Multi-Pass membrane Protein	Ca_v R-type, α-1E subunit, Each α_1 subunit consists of 6 helical transmembrane segments (S1-S6)	Modulation of firing patterns of neurons, Muscle Contraction, Hormone or neurotransmitter release, Cell Motility, Cell Division and Cell Death	Juvenile Myoclinic Epilepsy	(Schneider *et al.*, 1994) (Williams *et al.*, 1994) (Suzuki *et al.*, 2004)
	$Ca_V3.1$	CACNA1G	Neurons and Cardiac tissue	Multi-pass membrane protein	Ca_v T-type, α-1G subunit, Each α_1 subunit consists of 6 helical transmembrane segments (S1-S6)	Neuronal Firing Activity, Cardiac Pacemaker Activity	Epilepsy, Cardiac Hypertrophy	(Hagiwara *et al.*, 1988) (Huguenard, JR. 1996) (Tsakiridou *et al.*, 1995)
	$Ca_V3.2$	CACNA1H	Kidney, Liver, Heart, Brain	Multi-pass membrane protein	Ca_v T-type, α-1H subunit, Each α_1 subunit consists of 6 helical transmembrane segments (S1-S6)	Secretion of Neuroendocrine Prostate Cancer Cells, Contraction, Secretion Neurotransmission and gene Expression.	Epilepsy, Idiopathic generalized Type 6, Epilepsy, childhood absence 6 (ECA6)	(Splawski *et al.*, 2006)
	$Ca_V3.3$	CACNA1I	Brain Specific	Somato-dendritic Compartment of many Types of Neurones	Ca_v T-type α- 1I subunit, Each α_1 subunit consists of 6 helical transmembrane segments (S1-S6)	Electrical and Signaling, generate burst firing and Pacemaker Activity	Hyperalgesia	(Talley *et al.*, 1999) (Carbone and Lux., 1984) (Kim *et al.*, 2003)
	Ca_v β_1	CACNB1	Brain, Heart, Spleen, Central Nervous System & Neuro-blastoma Cell	Sarcolemma; Peripheral membrane protein	Ca_v L-type, β-1 (auxiliary)subunit	Modulating G protein inhibition and controlling the alpha-1 subunit membrane targeting	Malignant Hyperthermia susceptibility (Autosomal Dominant Disorder of Skeletal Muscle)	(Gregg et al.,1996)
	Ca_v β_2	CACNB2	Heart, Retina	Membrane of smooth Muscle	Ca_v L-type , β-2 (auxiliary) subunit	Hyperpolarizing Shifts	Lambert-Eaton Myasthenic Syndrome, Brugada Syndrome	(Perez-Reyes *et al.*,1992) (Pichler *et al.*, 1997) (Ball *et al.*, 2002) (Reimer *et al.*, 2000) (Singer *et al.*, 1991)
	Ca_v β_4	CACNB4	Brain, predominantly in the Cerebellum, Kidney	Vestibular, Cerebellar Neuronal membrane	Cav L-type , β-4 (auxiliary) subunit	Shifting the Voltage dependencies of activation and inactivation, Modulating G protein inhibition	Idiopathic generalized Epilepsy, Juvenile Myoclonic Epilepsy	(Xu *et al.*, 2011) (Ohmori *et al.*, 2008)

	Ca_v Υ_2	CACNG2	Brain	Multi-pass membrane protein	Ca_v Υ-2 (auxiliary)subunit	Regulates the trafficking and gating properties of AMPA-selective glutamate receptors	Mental Retardation	(Hamdan *et al.*, 2011) (Shi *et al.*, 2010) (Black and Lennon., 1999)
	Ca_v Υ_5	CACNG5	Epithelia	Cell Junction , Postsynaptic Cell Membrane	Ca_v Υ-5 (auxiliary)subunit	Modulates gating properties	Schizophrenia and Bipolar Disorder	(Chen RS. *et al.*, 2007) (Curtis *et al.*, 2011) (Chu *et al.*, 2001)

Table 3: Calcium ion channel subtypes in association with various diseases

3.2.4 Chloride Ion Channel

Chloride channel is the Cl^- ion conducting channel that can be categorized into five different types depending on the type of activators involved which are cAMP, Ca^{2+}, volume, voltage and ligand (Suzuki *et al.*,2006). Presently three well known gene families of Cl^- ions are ClC gene family, cAMP activated CFTR Cl^- channel gene family and ligand gated GABA, glycine-receptor chloride channel gene family (Jentsch *et al.*,2002). Different subtypes of this channel associated with diseases have been summarized in **Table 4.** These chloride channels play a variety of roles that are cell volume regulation, trans-epithelial transport, secretion of fluid from secretory glands and stabilization of membrane potential (Jentsch *et al.*,1995).

Channel Name	Subtypes	Genes encoding subtypes	Tissue Specificity	Sub cellular location	Subunit structure	Physiological Role	Involvement in disease	References
Chloride (Cl_v) Channel	Cl_vC1	CLCN1	Predominantly expressed in Skeletal Muscles	Multi-pass membrane protein	ClvC Type -1. Homodimer. Each monomer consist of 18 helical segments,	Membrane potential stabilization, Signal Transduction and Trans epithelial Transport	Autosomal Recessive Myotonia Congenita	(Koch *et al.*, 1992) (George *et al.*, 1993) (Lorenz *et al.*, 1994)
	Cl_vC2	CLCN2	Skeletal Muscle	Multi-pass membrane protein	ClvC Type -2. Homodimer. Each monomer consist of 18 helical segments,	Homeostasis in various Cells	Susceptibility to Epilepsy, Idiopathic generalized, Myoclonic Jerks	(Saint-Martin *et al.*, 2009) (Lamb *et al.*, 1999) (Jeworutzki *et al.*, 2012)
	Cl_vC3	CLCN3	Coronary Vascular Smooth Muscle Cells and Expressed at a Low level in Aortic Endothelial Cells	Multi-pass membrane protein	ClvC Type -3, Homo- or heterodimer. Each monomer consist of 18 helical segments,	Neuronal cells to establish short-term Memory, Myoclonic Jerks	Juvenile absence Epilepsy Type 2, Idiopathic generalized Epilepsy	(Cid *et al.*, 1995) (Lamb *et al.*, 1999)
	Cl_vC6	CLCN6	Testis, Ovary, Small intestine, Brain and Skeletal Muscle.	Endosome membrane	——	Antiporter and Contributes to the Acidification of the Lysosome Lumen	Lysosomal storage disease	(Ota *et al.*, 2004) (Brandt and Jentsch., 1995) (Eggermont *et.al.*, 1997) (Lamb *et al.*, 1999) (Ignoul *et al.*, 2007) (Poet et al., 2006)
	Cl_vC7	CLCN7	Brain, Testis, Muscle and Kidney.	Lysosome membrane; Multi-pass membrane protein	ClvC Type -7. Heteromers of α -(CLCN7) and β-(OSTM1) subunits.	Antiporter and Contributes to the Acidification of the Lysosome Lumen	Infantile Malignant, Osteopetrosis Type 2, Albers-Schonberg, Disease or Marble Disease	(Schroeder *et al.*, 2007) (Graves *et al.*, 2008) (Leisle *et.al.*, 2011) (Kornak *et al.*, 2001)
	$Cl_{Ca}1$	CLCA1	Small Intestine, Colon, Goblet Cells Testis and Kidney	Localized to Microvilli, Basal Crypt Epithelia, Peripheral membrane protein; Extracellular side	——	Goblet cell, Metaplasia, Mucus Hyper secretion, Cystic Fibrosis and AHR	Biomarker in Chronic Asthma., Chronic Obstructive Pulmonary Disease	(Gruber *et al.*, 1998) (Bustin *et al.*, 2001) (Hoshino *et al.*, 2002) (Toda *et al.*,2002) (Lee *et al.*, 2005) (Gibson *et al.*, 2005)
	$Cl_{Ca}2$	CLCA2	Epithelium including Cornea, Esophagus, Larynx,	Single-pass type I membrane protein. Basal cell membrane; Single-pass type I membrane protein	——	May act as a Tumor suppressor in Breast and Colorectal Cancer, Cell Adhesion	Leukemia, Breast Tumor Suppressor Gene	(Gruber *et al.*, 1999) (Bustin *et al.*, 2001) (Abdel-Ghany *et al.*, 2001) (Connon *et al.*, 2005) (Connon *et al.*, 2006)

Table 4: Chloride ion channel subtypes in association with various diseases

3.3 Molecular Entities of Ion Channels

3.3.1 Sodium Channel Structure

Voltage gated sodium (Na_v) channel is a complex of a 260kDa (α-subunit) and 33–36 kDa (β1–β4 auxiliary subunits; Casadei *et al.,* 1986). Pore forming single α-subunit has been associated with four β-subunits [**Figure 4(a)]**. The α-subunit has four internally repeated domains (I-IV) that mold themselves to form an ion traversing pore. Furthermore each domain carries six trans-membrane helical segments designated as S1-S6 in which uncovered segment (S4) serves as voltage sensor along with a loop between S5 and S6 (Noda *et al.,* 1984; Catterall *et al.,* 2008). Apart from α-subunit that has a role in pore formation; β-subunits have an important role of modulation in the kinetics of gated channels that cause positive or negative shift upon voltage sensitivity of the channel depending on its type. Pore forming α- subunit mutation is responsible to majority of neurological channelopathies whereas mutations in auxiliary subunit have been known to be responsible in few cases (Fontaine *et al.,* 1990; Rojas *et al.,* 1991; Ptacek *et al.,* 1992).

3.3.2 Potassium Channel Structure

Potassium channels primarily consist of four α-subunits surrounding the central pore region frequently associated with auxiliary β-subunit **[Figure 4(b)]**. Each α-subunit of voltage gated potassium channel (K_v) comprised of six transmembrane helical segments (S1-S6) with a cytoplasmic N and C-termini. N-terminus have T1 domain (tetramerization domain) that assembles the α-subunits into functional channel (Zerangue *et al.,* 2000; Bocksteins *et al.,* 2009) while S4 segment is highly positive and acts as voltage sensor along with the loop between S5-S6 (Yost, CS. 1999). Pore region contains the signature sequence GYG which has specificity for conducting K^+ ions (Bocksteins *et al.,* 2009). Auxiliary β-subunit assembles into tetrameric structures and interacts with α-subunit of K_v channel which provide a role in modulating channel gating kinetics (Gulbis *et al.,* 1999). Apart from that an additional long C-terminal extension in α-subunit has found in case of calcium activated potassium channels whereas inward rectifier potassium channel's α-subunit is composed of only two transmembrane segments S1 and S2 which resembles with the S5 and S6 segments of voltage gated potassium channel (Yost, CS 1999). The β-subunit that associate with α-subunit of calcium sensitive potassium channel has two transmembrane segments which increases calcium sensitivity of the channel while β-subunit that associate with α-subunit of inward rectifier potassium channel has comprised of several transmembrane segments (Benatar, M. 2000).

3.3.3 Calcium Channel Structure

Calcium channel consists of a core α_1 subunit and other auxiliary subunits like β, α_2, δ and γ subunits (Arikkath and Campbell., 2003;**[Figure 4(c)]**. Ca^{2+} ion conduction is carried out by a transmembrane protein that is α1 subunit which possesses molecular mass of nearly 200-260kDa. The α1-subunit consists of four transmembrane repeating units, where each unit is comprised of six helical segments S1-S6. S4 helix serve as voltage sensor while glutamate ions present in the linker region of S5 and S6 are the key residues responsible for providing selectivity filter role to the channel. Besides

this ion conduction tunnel is formed by the combination of S5 segment, linker region between S5-S6 and S6 segment from each of the four transmembrane units (Catterall and Curtis, 1987; Campbell *et al.*, 1988; Catterall, WA. 1988; Bergsman *et al.*, 2000). The β-subunit is a peripheral membrane unit of nearly 60kDa which is associated with cytoplasmic surface of membrane and is responsible for differences in major classes of calcium channel (L-, N-, P/Q-type, etc.; Takahashi *et al.*, 1987; Bergsman *et al.*, 2000). Moreover α_2-δ is a 175 kDa dimer which is linked by a disulfide bridge and is responsible for modulating channel gating kinetics (De Jongh *et al.*, 1990; Klugbauer *et al.*, 1999). Another accessory γ-subunit is known to provide the inactivating property in few cases (Eberst *et al.*, 1997; Letts *et al.*, 1998).

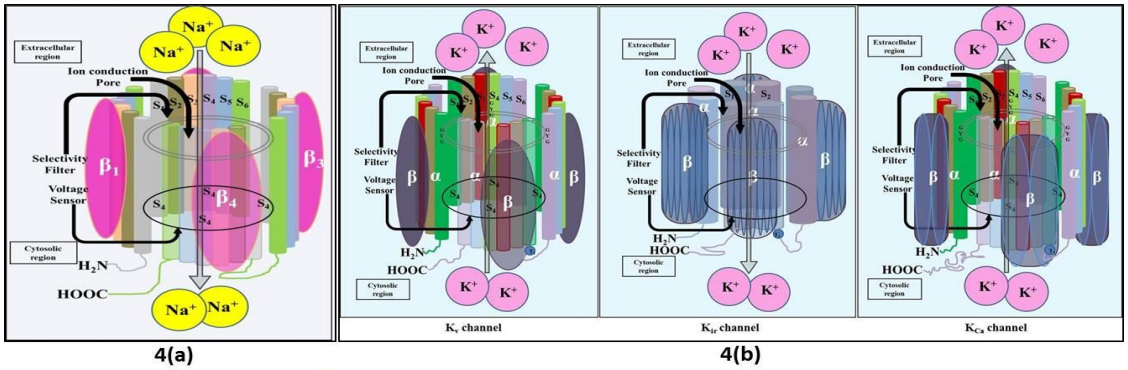
3.3.4 Chloride Channel Structure

Different gene families of Chloride channel have different structures for conducting Cl^- ions.

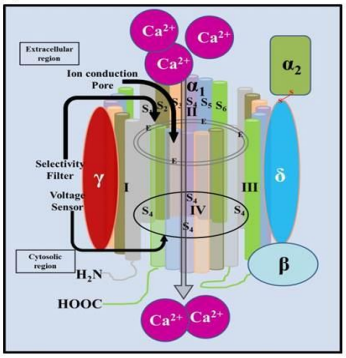
3.3.4.1 ClC-chloride channel or voltage gated Chloride channel has a double barrel structure **[Figure 4(d)]** (Miller and White., 1984; Jentsch *et al.*, 2002). These chloride channels are homodimers and a pore is formed by each subunit. Each subunit exhibits an anti-parallel architecture. Each subunit contains 18 α-helices (Dutzler *et al.*, 2002)**.**

3.3.4.2 CFTR chloride channel is comprised of two motifs. Each motif contains a membrane spanning domain (MSD) and nucleotide binding domain (NBD). R (regulatory) domain act as a connecting link between these two MSD-NBD motifs (Sheppard and Welsh., 1999). MSD usually comprised of six transmembrane segments and NBD has a role in interacting with ATP (Hyde*et al.*, 1990).

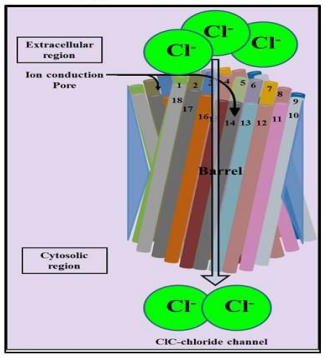
3.3.4.3 Ligand gated chloride channel consists of five subunits. Each subunit comprised of long N-terminal extracellular domain, four putative transmembrane domains (TM) and a short extracellular C-terminal. N-terminal domain has conserved Cys-loop (Maricq *et al.*, 1991; Lindstrom *et al.*, 1995; Vannier and Triller., 1997).



4(a) 4(b)



4(c)



4(d)

Figure 4: (a) Sodium channel structure: α-subunit of voltage gated sodium channel comprised of tetradomain where each domain consists of internally repeated transmembrane helical segments (S1–S6) that is associated with four auxiliary β-subunits. **(b) Potassium channel structure:** α-subunit comprised of transmembrane helical segments that is arranged in a tetramer manner and associated with auxiliary β-subunit. **(c) Calcium channel structure:** In a voltage gated calcium channel α1-subunit arranges itself in a tetradomain manner where each domain consists of six helical transmembrane segments that is associated with other auxiliary subunits α2-δ (disulfide linkage), β and γ. **(d) Chloride channel structure:** Voltage gated chloride channel have double barrel antiparallel structure where each barrel comprised of 18 helical transmembrane segments.

3.4 Ion Channels and Neurological Diseases

Action-potential generation and synaptic transmission in the central and peripheral nervous system depends on the co-ordinated activity of voltage-gated ion channels. They are found to be present on axon hillock, node of Ranvier in case of myelinated and in non-myelinated neurons as well (Debanne *et al.,* 2011). Another salient feature of these channels is related to its highly conserved structure during the evolutionary process. However, synonymous mutation sites in trans-membrane region are more conserved than the non-trans-membrane region but mutations in non-trans-membrane region are also reported to be non-neutral ultimately causing channel dysfunction (Zhou *et al.*,2012). Nonfunctional ion channels are incompatible for the cellular entities and leads to the generation of varieties of neurological diseases.

3.4.1 Sodium Ion Channelopathies With Molecular Mechanism

3.4.1.1 Potassium-Aggravated Myotonia (PAM)

PAM can be categorized into three different clinical phenotypes; myotonia fluctuans, severe myotonia permanens and acetazolamide responsive myotonia that follow autosomal dominant inheritance pattern (Orrell*et al.*,1998) and categorized under rare disease by the Office of Rare Diseases (ORD), National Institute of Health (NIH). Myotonia implies muscle stiffness followed by its inability to relax while in PAM myotonia worsened in the presence of potassium ions. It begins either in childhood or adolescence and known to be caused due to alteration in $Na_v1.4$ channel α-subunit as a result of mutations in SCN4A gene (Heine *et al.*, 1993; Orrell *et al.*, 1998; Vicart *et al.*, 2005). Mutated channel lead to the enhanced influx of sodium ion movement in muscle and thus prolonged contraction has been observed in PAM. There are multiple factors responsible for its triggering for instance, fasting, physical exercise, voluntary contraction, cold weather, fever and potassium rich food (Ptacek *et al.*,1992). However, in PAM, potassium ion promotes the muscle contraction and therefore intake of potassium rich food is not advisable. Severity of symptoms might be exacerbated when cramps occur in respiratory muscle which could lead to hypoxia. The affected patients exhibit same phenotype with little clinical variation which has been confirmed by electromyography (Lerche *et al.*, 1993). Multiple reasons that have been suggested for the alteration of channel function in several myotonias are reduced fast channel inactivation, enhanced recovery rate from fast inactivation, slowed deactivation or hyperpolarizing shift in steady state activation (Cummins and Bendahhou, 2009). The above phenomenon were also reported in a recent study of Na_v 1.4 mutation i.e. A799S (Lion-Francois *et al.*, 2010) in a patient suffering with

severe neonatal episodic laryngospasm (Simkin *et al.,* 2011). In another study using patch clamp technique, it has been reported that heterozygous mutations (G1306V, G1306A, G1306E) in same codon of SCN4A gene, is very crucial for sodium channel inactivation (Lerche *et al.,*1993). Apart from fewer intakes of potassium rich foods, other treatments like physiotherapy (stretching or massaging to aid muscle relaxation) and certain medications such as mexiletine, carbamazepine, or acetazolamide is useful.

3.4.1.2 Para Myotonia Congenita (PMC)

PMC is a myopathy condition that affects the skeletal muscle contraction and tone that result in stiffness along with sustained weakness for hours. However, the onset of prolonged muscle contraction begins in infant while episodes of weakness start at adolescence stage. This disease is also known as Eulenberg disease and comes under rare congenital autosomal dominant neuromuscular disorder (Haass *et al.,*1981). It is highly cold sensitive and exacerbated due to exercise and cold temperature which affect upper bodily parts for instance bulbar, facial, neck and hand muscles more than the lower limbs (Magee, KR. 1966). Prolonged cry in such patients often lead to blepharospasm. Not always but frequently PMC patients are found to be accompanied by Hyperkalemic periodic paralysis with increased level of serum creatine kinase. Voltage gated sodium channel α-subunit encoding SCN4A genetic mutation is responsible for PMC (Kim *et al.,* 2002; Pereon *et al.,* 2003) where the cytoplasmic loop region between segment III and IV in sodium channel is hotspot for the mutation (McClatchey *et al.,* 1992; Ptacek *et al.,* 1992; Lerche *et al.,* 1993; Ptacek *et al.,* 1993; Sasaki *et al.,* 1999; Okuda *et al.,* 2001). It has also been studied that R1448H mutation causes cold induced myotonia that leads to PMC and is responsible for slowed inactivation and faster recovery from inactivation as compared to non-mutant channels (Mohammadi *et al.,*2003). The problem of myotonia in PAM patients can be relieved by administering mexiletine as a first line agent while episodic weakness can be treated with daranide or dianox.

3.4.1.3 Hyperkalemic Periodic Paralysis (HYKPP)

Hyperkalemic periodic paralysis is a congenital autosomal dominant genetic disorder (Ptacek *et al.,*1991) with elevated potassium level in blood that causes episodes of muscle weakness (Venance *et al.,*2006) where intake of potassium rich foods and rest after exercise are the most prominent factors for triggering of HYKPP. The attack lasts for few hours to a day where its severity is specified via membrane inexcitability and muscle weakness which affects shoulder, hips more often than hands and legs (Weber *et al.,* 2006; Webb and Cannon, 2008). Underlying SCN4A gene mutations affect inner core of transmembrane segments or intracellular protein loops which inturn impair the anchoring site of fast inactivation particle thereby leading to persistent Na^+ current through unclosed sodium channel (Bendahhou *et al.,* 2002). The persistent sodium current across non inactivated channel causes depolarization of cell thereby inactivating other normal sodium channels due to inability of action potential generation (Cannon *et al.,*1991; Lehmann-Horn *et al.,*2002). Patients suffering from this disease, report abnormal muscle biopsy with high level of creatine

kinase in the serum and permanent muscle weakness with aging. The treatment focuses on relieving symptoms and preventing further attacks which could be accomplished with the help of low potassium-high carbohydrate meal and medication of acetazolamide and hydrochlorothiazide drugs which are effective with minimal risks (McArdle, B. 1956; Han *et al.*,2011).

3.4.1.4 Primary Erythro-Melalgia (PEM)

Primary erythro-melalgia is an autosomal dominant, peripheral nerve pain disorder which can be characterized by severe burning and bilateral pain with swelling in extremities of the body especially in hands and feet (Dib-Hajj *et al.,* 2005; Waxman and Dib-Hajj., 2005a & b). Due to micro-vascular arteriovenous shunting in PEM patients, vasomotor changes such as erythema and oedema takes place, resulting in the pain sensation around affected area (Mork *et al.,* 2000). The episodic attacks are found to be triggered or aggravated by increased body temperature, spicy food and exercise while cold environment relieves the pain (Michiels *et al.,* 2005). Mutations in SCN9A gene is responsible for pathogenesis of PEM that causes alteration in $Na_v1.7$ α-subunit and leads to increased action potential (Cummins *et al.*,2004) thereby causing prolonged transmission of pain signals (Yang *et al.*,2004; Dib-Hajj *et al.*, 2005; Drenth*et al.*,2005; Dib-Hajj *et al.*,2007). The patch clamp analysis of mutated sodium channel revealed that there is a hyperpolarization shift toward activation of the channel and slowed inactivation kinetics that makes opening of channel easier and prolonged (Cummins *et al.*,2004). Various treatment modalities have been tried viz. aspirin, cyclosporine, beta blockers, calcium channel antagonists but patient should take preventive measures along with medication which include sodium channel blocker like ranolazine and mexiletine with highly promising results (Iqbal *et al.,* 2009).

3.4.1.5 Paroxysmal Extreme Pain Disorder (PEPD)

PEPD is an autosomal dominant peripheral neuropathy that was earlier known as familial rectal pain and is characterized by excruciating pain and flushing in the submandibular, ocular and rectal region (Fertleman and Ferrie., 2006). Recurrent pain and skin flushing begins in childhood and pain progresses to ocular and mandibular region with age. Although PEPD is a lifelong disorder but the frequency of attack generally decreases with age. Moreover it has been observed that attacks are provoked by physical trigger like crying, eating and defecation (Pett *et al.,* 2013). PEPD is caused due to functional gain mutation in SCN9A gene (Choi *et al.,* 2011; Estacion *et al.,* 2011; Fischer and Waxman, 2010) that means mutated channel results in sustained flow of sodium ion and hence maintaining action potential which prolongs transmission of pain signals. It has been reported that mutated channel lowers the threshold for single action potential in dorsal root ganglion neurons that results into increased number of action potential in response to a supra-threshold stimuli which leads to elevated pain signal transmission (Dib-Hajj *et al.,* 2008). To relieve the pain it is important to take preventive measure from triggering factor like managing constipation and use of anticonvulsants for instance, carbamazepine has been found to be very effective in many patients (Theile and Cummins, 2011).

3.4.1.6 Congenital Insensitivity to Pain (CIP)

CIP is an autosomal recessive peripheral sensory neuropathy characterized by complete loss of pain sensation in response to injuries (Danziger and Willer., 2009) and also known as congenital analgia or congenital analgesia, congenital asymbolia and congenital indifference to pain (Dyck *et al.*,1983). Congenital insensitivity to pain has been classified to the family of Hereditary Sensory and Autonomic Neuropathies (HSAN) and it has two common occurring forms that are congenital insensitivity to pain (CIP) and congenital insensitivity to pain with anhidrosis (CIPA) which has been classified as HSAN-V and HSAN-IV respectively. CIP has been observed to be prevalent in children born to consanguineous marriages and they generally suffers from accumulated wounds due to repeated injuries as a consequence of imperceptions of pain sensation (Protheroe, SM. 1991). Earlier, it was reported that CIP patients possess only nonsense mutations in the SCN9A gene (Dabby, R. 2012; Cox *et al.*, 2006) which were responsible for truncated α-subunit of sodium channel ($Na_v1.7$) but recently missense mutation (R896Q), frame shift deletion mutation (ΔR1370-L1374) and splicing mutation (IVS8-2A>G) have also been observed (Cox *et al.*,2010; Klein *et al.*,2013). Recent mutation were reported to be associated with pore regions thereby causing defect in the ion conduction through $Na_v1.7$ channel present on nociceptors that lead to complete loss of pain signal transmission from site of injury to brain (Fischer and Waxman, 2010; Lampert *et al.*,2010; Goldberg *et al.*,2007). CIP patients not only exhibit loss of pain sensation but sometimes smell sensation as well because $Na_v1.7$ channel is also present on olfactory receptor neurons that can lead to anosmia (Weiss *et al.*, 2011). Convincing treatment for this disease is remain unclear but case reports showed promising result with the use of naloxone and naltrexone in reversing the effect of analgesia (Protheroe, SM. 1991).

3.4.1.7 Generalized Epilepsy with Febrile Seizures (GEFS)

Epilepsy is a chronic neurological disorder that can be characterized with the recurrent episodes of convulsions and sensory disturbances due to abnormal electrical signals in the brain. Generalized epilepsy with febrile seizures (GEFS) is a recently described autosomal dominant epileptic syndrome where convulsions are associated with the elevated temperature of the body (Chang and Lowenstein, 2003). It begins in childhood (1month to 1 year) and may last upto the age of 6 years or sometimes continues till the onset of puberty. GEFS patient exhibit a variety of clinical phenotypes that are typical febrile seizures and other seizure types such as tonic-clonic, myoclonic, myoclonic-astatic, absences, or atonic seizures (Scheffer and Berkovic, 1997). Simple febrile seizure generally lasts for 15 minutes while complex febrile seizure exhibit episodes that lasts more than 15 minutes and it has also been observed that epilepsies become more prominent in aged people (Brodie *et al.*,2009). In most of the cases majorly mutations were found in SCN1A, SCN1B gene and γ2 subunit of $GABA_A$ receptors (Meisler*et al.*,2010; Wallace*et al.*,1998; Wallace*et al.*,2002; Audenaert*et al.*, 2003; Meisler and Kearney, 2005; Fujiwara, T. 2006; Kang *et al.*,2006) where few mutations in $Na_v1.1$ causes mild epilepsies but several mutations in $Na_v1.1$ channel leads to severe epilepsies (Catterall*et al.*, 2010).The resulting seizures are found to be familial in few cases and sporadic in other cases that

imply environmental factors like elevated temperature also play a contributing role. Hyperthermia itself is capable of generating seizures while resulting mutations are known to aggravate the susceptibility of developing a seizure with fever (Dube *et al.,* 2009). Generally regular medicines are not prescribed for such patients but for severe cases epileptic medicines like sodium valproate, ethosuximide, clobazam, carbamazepine and phenytoin drugs are helpful in controlling epilepsies (Tate *et al.,*2005; 2006; Scheffer *et al.,*2007; Groot *et al.,*2012).

3.4.2 Potassium Ion Channelopathies With Molecular Mechanism

3.4.2.1 Paroxysmal Dyskinesia

Paroxysmal dyskinesia is an autosomal dominant rare episodic movement disorder that exhibit abnormal involuntary movements including chorea, dystonia only during attacks (Demirkiran and Jankovic., 1995). It has been classified into four different types on the basis of triggering factors responsible for the episodes that are (i) Paroxysmal kinesigenic dyskinesias (PKD) which is known to be triggered by sudden voluntary movements and unexpected stimulus, (ii) Paroxysmal non-kinesigenic dyskinesias (PNKD) that can be triggered by factors other than movement like stress, fatigue and alcohol consumption, (iii) Paroxysmal exercise (exertion) induced dyskinesias (PED) which could be triggered by prolonged exercise and lastly (iv) Paroxysmal hypnogenic dyskinesias (PHD) in which attack can be triggered during Non-rapid eye movement sleep (Unterberger and Trinka, 2008). Increased studies revealed that familial PKD can be caused by channel mutations and it has been identified that coexistence of generalized epilepsy and paroxysmal dyskinesiais caused by mutations in KCNMA1 gene. The resulting mutation in this gene promotes excitability of neurons by inducing rapid repolarization of action potential which allows neurons to conduct at a faster rate thereby causing recurrent attacks (Du *et al.,* 2005). Moreover recent studies identified that PKD is linked to pericentromeric region of chromosome 16 in a number of families and PNKD is caused due to mutation in myofibrillogenesis regulator 1 gene (MR-1) on Chromosome 2 while PED is caused due to mutation in glucose transporter gene (GLUT1; Mehta *et al.,*2009).There is no cure for paroxysmal dyskinesia but symptoms can be relieved to some extent inconsistently with the help of anticonvulsants drugs like acetazolamide, anticholinergics, levodopa and tetrabenazine along with avoiding the precipitating events like prolonged exercise(Mehta *et al.,*2009; van Rootselaar *et al.,*2009).

3.4.2.2 Benign Familial Neonatal Seizure (BFNS)

BFNS is an autosomal dominant inherited form of epilepsy which has been characterized by recurrent seizures in new born babies that causes muscle stiffness, convulsions and loss of consciousness (Biervert*et al.,* 1998). In majority of the suffering neonates seizures began within the first week of life and disappeared spontaneously within a few months but some patients showed dysfunctional channel even in adulthood (Tomlinson *et al.,* 2012). Multiple mutations have been reported in KCNQ2 and KCNQ3 gene in the patients suffering with BFNS thereby generating altered M-current (Singh *et al.,* 1998; Castaldo *et al.,* 2002, Singh *et al.,* 2003). However, normal M-current generated by $K_v7.2$ and K_v 7.3potassium channel

repolarize the cell and hence ensures the inactivation of neurons while mutated channel generates reduced or altered M-current that causes over-activation of neurons which leads to the seizure development in brain (Wang *et al.*,1998; Soldovieri *et al.*,2007; Volkers *et al.*,2009). Anticonvulsant therapy has been widely used where phenobarbital is effective in majority of individuals while some individual may require other epileptic drug like carbamazepine, phenytoin, valproic acid, clonazepam, midazolam or vigabatrin but treatment has not had a consistent effect on the duration of seizures (Soldovieri *et al.*,2007).

3.4.2.3 Andersen Tawil Syndrome (ATS)

ATS is an autosomal dominant genetic disorder that has been characterized by periodic paralysis, ventricular arrhythmias and developmental abnormalities typically affect head, face and limbs(Tawil *et al.*,1994). Based on the genetic causes ATS has been classified into two types where mutated KCNJ2 gene (Inward rectifier potassium channel $K_{ir}2.1$) was responsible for ATS type 1 while genetic cause for ATS type-2 is still unknown (Plaster *et al.*,2001). Its onset generally takes place around 20 years and 70% of KCNJ2 mutations exhibit prolonged QT interval thereby also classified as Long QT syndrome 7 (Tristani-Firouzi *et al.*,2002) but a distinctive electrocardiogram have been observed in ATS1 patients with prolonged terminal T wave and prominent enlarged U waves (Zhang *et al.*,2005). Altered $K_{ir}2.1$ inward rectifier potassium channel disrupts PIP2 (phosphatidylinositol-4,5-bisphosphate) binding which has been responsible for inactivating channel thereby leading to sustained action potential and hence causes periodic paralysis and arrhythmias in skeletal and cardiac muscles (Lopes *et al.*,2002, Seebohm *et al.*,2012). Treatment of ATS patients require closely coordinated expertise between a neuromuscular specialist and a cardiologist. However it has been observed that drugs may have beneficial effect on one tissue while detrimental on other but amiodarone and acetazolamide are effective in many cases (Junker *et al.*,2002).

3.4.2.4 SeSAME and EAST Syndrome

SeSAME/EAST is an autosomal recessive disorder whose nomenclature is based on the characteristic symptoms they exhibit, for instance SeSAME patients are affected with seizures, sensorineural deafness, ataxia, mental retardation and electrolytic imbalance (hypokalemia, metabolic alkalosis, and hypomagnesaemia; Scholl *et al.*,2009) whereas EAST patients possesses typical symptoms that are epilepsy, ataxia, sensorineural deafness and tubulopathy (Bockenhauer *et al.*,2009). Both of them are known to be caused due to mutations in KCNJ10 gene that codes for ATP-sensitive inward rectifier potassium channel 10 (K_{ir} 4.1 channel; Freudenthal *et al.*,2011). It has been reported that K_{ir} 4.1 channel is expressed in the brain, inner ear, retina, and kidney thereby imparting the functional loss in these organs with mutations. In brain it contributes potassium buffering for glial cells, controls neuronal excitability and maintains systemic potassium ion homeostasis while in kidney it maintains electrolytic balance across distal convoluted tubule (Williams *et al.*, 2010). Multiple mutations in KCNJ10 gene has been reported, that alters inactivation of Kir 4.1 channel via loosing affinity towards channel modulator like PIP2 that results in

reduced channel activity with prominent symptoms (Sala-Rabanal *et al.*,2010). They are lifelong disorders and there is no current treatment that can cure the condition but we can use anti-epileptic medicines to relieve symptoms under the guidance of a nephrologist.

3.4.2.5 Jervell and Lange-Nielson Syndrome (J-LN)

J-LN is an autosomal recessive most severe variant of long QT syndrome that has been characterized by congenital sensorineural hearing loss and cardiac arrhythmia. It begins in childhood and patient suffers with deafness, recurrent fainting, ventricular arrhythmia and sometimes sudden death(Schwartz *et al.*,2006).Voltage-dependent slowly activating delayed rectifier potassium channel coding KCNQ1 (α-subunit) and KCNE1 (β-subunit) genetic mutations were reported in the J-LN patients that are responsible for potassium ion imbalance in the inner ear cochlear hair cells and cardiomyocytes (Chen *et al.,* 1999; Tyson *et al.*,2000). For normal hearing, a continuous flow of endolymph is required into the cochlear hair cells that are known to maintain the voltage gradient for nerve signal transmission (Lasak *et al.,* 2014), thus mutated channel disrupts the voltage gradient required for transmitting signal through auditory nerves thereby causing deafness. On the other hand, mutated channels in cardiomyocytes exhibit delayed repolarization thereby causing prolonged QT wave responsible for cardiac arrhythmia (Lehnart *et al.,* 2007). There is no cure for J-LN but as a relieving therapy beta blockers are being used to keep heart beat under control with a limited efficacy. Moreover automatic defibrillator and cochlear implantation techniques are also being used for treating cardiac arrhythmia and hearing loss respectively in case medication fails but patients are highly prone to sudden death (Rocha *et al.,* 2013; Broomfield *et al.,* 2012).

3.4.2.6 Cardiac Arrhythmia

Cardiac arrhythmia is an abnormal heartbeat related disorder that can be characterized by dizziness, palpitations, syncope, breathlessness and *angina*. Arrhythmias can be classified on the basis of two factors that are their origin (atria or ventricle) and heart rate where heartbeat might be very slow (bradycardia), very fast (tachycardia), quite early (premature contraction) and quite irregular (fibrillation; Fenton *et al.*,2008). Voltage gated ion channels are responsible for the electrical conductivity in the heart and it has been reported that defects in expression and function of ion channels are responsible for certain types of arrhythmias (Kirsch, GE. 1999).In most of the studies KCNE1, KCNE2, KCNH2, KCNQ1, KCNJ2 and SCN5A genetic mutations were identified in the patients suffering from various kinds of cardiac arrhythmia (Schott *et al.*,1999; Tsuboi and Antzelevitch., 2006; Moss *et al.*,2007; Tsai *et al.*,2008). These genetic mutations are responsible for altering the inward rectifying voltage gated potassium channel and voltage gated sodium channel respectively that leads to various phenotypic consequences of these mutations like Brugada syndrome (BrS, a form of idiopathic ventricular fibrillation), Lev-Lenegre syndrome (familial progressive conduction disease), Long QT syndrome (LQTS), Short QT syndrome (SQTS) and Familial atrial fibrillation (AF) (Campuzano *et al.*,2010). There are three mechanisms that have been proposed by different research groups for explaining the

pathogenesis of cardiac arrhythmias (Gaztanaga *et al.*,2012) that are (i) Automaticity; where enhanced or suppressed firing of impulse takes place by cardiac muscle cells (Weller and Noone., 1989), (ii) triggered activity; which involves impulse initiation due to the membrane potential oscillations occurring just after an action potential that results in abnormal transmission of electrical impulse in the heart cell thereby causing aberrant cardiac rhythm. This mechanism has been widely accepted to be related with the ion channel mutations (Charpentier *et al.*,1991) and (iii) Re-entry; it takes place when isolated fibers have not been activated during initial wave of depolarization but get excited before dying of previous impulse which in turn can re-excite those area which have already recovered from initial depolarization (Zipes, DP. 2003). Beta blockers can relieve the symptoms to some extent depending on the severity of arrhythmia.

3.4.3 Calcium Ion Channelopathies With Molecular Mechanism

3.4.3.1 Spino-Cerebellar Ataxia type-6 (SCA6)

There are more than 25 types of spino-cerebellar ataxias that are known to affect cerebellum, brainstem and other parts of central nervous system but among them SCA6 is one of the most common occurring that affects only cerebellum. SCA6 is an autosomal dominant progressively degenerative pure cerebellar ataxia that is characterized by poor coordination of hands, speech, eye movements and progressive loss of physical control (Paulson, HL. 2009). CACNA1A genetic mutation has been reported (Rajakulendran *et al.*,2010) where expansion of CAG repeats were found at the 3' region that generates poly glutamine tract thereby producing abnormally extended α_1 subunit of calcium channel (Ishiguro *et al.*,2010). These poly glutamine residues have been responsible for abnormal aggregation of calcium channel protein thereby affecting calcium ion transport which imparts toxicity to the neurons for instance altered release of neurotransmitters in the brain eventually leads to the neuronal death (Purkinje cells; Kordasiewicz and Gomez. 2007). However very limited clinical trials have been done for disease prevention but a recent study showed the beneficial effect of lithium in treating SCA1 (Watase *et al.*,2007). Apart from that acetazolamine can be used to eliminate episodes of ataxia and RNA antisense approach can also be tried to decrease the expression of mutant gene product (Xia *et al.*, 2004).

3.4.3.2 Hypokalemic Periodic Paralysis (HypoPP)

Hypokalemic periodic paralysis is an autosomal dominant paralytic disorder that can be characterized by recurrent attacks of extreme muscle weakness associated with low potassium levels in serum. In general, the attacks last for several hours but sometimes it last for several days that can be precipitated by a variety of factors for instance, sodium-rich food, carbohydrate load, cold temperature, infection, stress, anesthesia and rest after exercise (Sternberg *et al.*,2002). Major impact (upto 60%) in the pathogenesis of Hypo PP is contributed by CACNA1S genetic mutations that can be followed by mutations in SCN4A and KCNE3 gene (Jurkat-Rott *et al.*, 1994; Abbott *et al.*, 2001; Sternberg *et al.*, 2001; Matthews *et al.*, 2009). Most of the underlying mutations in sodium channel were reported to nullify the outermost positively charged

arginine or lysine residues of a voltage sensor, for instance, multiple mutations in $Na_v1.4$ channel were present in the voltage sensor region (S4) of domain I, II and III (Jurkat-Rott *et al.*,2000).The homologous location of S4 missense mutations in $Ca_v1.1$ channel associated with HypoPP has led to the conclusion that abnormal gating pore current is the common underlying mechanism of mutated sodium and calcium channel for the progression of HypoPP (Wu *et al.*,2012).However, the known mutations affect the voltage sensing capability of these channels which are responsible for the deregulated flow of Ca^{2+} and Na^{+} ions into the muscles that cause reduced contractibility of muscles and ultimately muscle weakness (Sokolov *et al.*,2007). However it is quite difficult to treat HypoPP but we can prevent the attacks by regulating sodium and potassium intake. Moreover acetazolamide has been found to be very effective in preventing paralytic attacks among 50% of the cases (Matthews *et al.*,2011).

3.4.3.3 Episodic Ataxia (EA)

Episodic ataxia is a group of related autosomal dominant disorders that have been characterized by episodes of impaired, uncoordinated bodily movements that can eventually cause muscle stiffness and cramps (Jen *et al.*,2007). These symptoms are generally begins in adolescence and period of attacks usually last from hours to days depending on its severity. EA has been classified into seven types i.e. EA-1 to EA-7 based on their various characteristics which include sign, symptoms, attacking period and onset age, moreover out of these seven types only episodic ataxia type 2 and 5 are known to be associated with calcium channel mutations. It have been reported that KCNA1, CACNA1A, CACNB4 and SLC1A3 genetic mutations are responsible for the occurrence of episodic ataxia type 1, 2, 5 and 6 respectively while genetic cause for EA-3,4 and 7 are still unknown(Adelman *et al.,* 1995; Escayg *et al.*,2000; Imbrici *et al.,* 2005; Jen *et al.*,2005). The underlying CACNA1A and CACNB4 genetic mutations have been responsible for down regulating the Ca^{2+} transport that prevents the release of neurotransmitters into the brain thereby disrupting the signals (Wan *et al.,* 2005). Similarly decreased transport of K^{+} ions due to KCNA1 genetic mutations add over excitability to the neurons (Maylie *et al.*,2002) while SLC1A3 genetic mutant glutamate transporter loses its ability to remove glutamate from synaptic region which further provides excitation to the neurons. Thus altered channels disrupt the normal signaling that triggers episodes of ataxia. The frequency and severity of attacks can be relieved by using antiepileptic drugs and carbonic anhydrase inhibitors for instance carbamazepine, valproic acid and acetazolamide are found to be effective in episodic ataxia type-1 (Eunson *et al.,* 2000; Klein *et al.,* 2004).

3.4.3.4 Familial Hemiplegic Migraine (FHM)

Familial hemiplegic migraine is an autosomal dominant familial migraine that usually occurs in a particular part of the head preceded by neurological symptoms like double vision, blind spot or flashing lights (Jen, JC. 2001). FHM has been classified into three forms on the basis of clinical or descriptive criteria and can be triggered by emotional stress, certain foods and minor head injury. It has been reported that mutations in CACNA1A, ATP1A2 and SCN1A genes are the prevalent causes for

FHM type-1, FHM type-2 and FHM type-3 respectively (Ophoff *et al.*,1996; De Fusco *et al.*,2003; Dichgans *et al.*,2005a). Mutated CNCNA1A gene that encode $Ca_v2.1$ channel get activated more easily than usual thereby leading to more influx of Ca^{2+} ions which in turn promote excessive release of neurotransmitters which impart strong signals for severe headache and lead to FHM type-1 (Dichgans *et al.*,2005b). While in case of FHM type-2, mutated ATP1A2 gene forms either altered or truncated Na^+/K^+ ATPase protein that prevent the flow of K^+ ions out of the neurons thereby causing sustained release of neurotransmitters at the neuronal junction and thus prolongs excitation of pain signals (De Fusco *et al.*,2003). Moreover altered $Na_v1.1$ channel encoded by mutated SCN1A gene has also reported to exacerbate headache in a similar fashion as were in case of mutated calcium channel. Thus resulted mutations in these genes causes FHM due to increased release of neurotransmitters in response to imbalanced ion flow (Pietrobon, D. 2007). Treatment of hemiplegic migraine is quite challenging but apart from anecdotal; verapamil and acetazolamide have shown significant effect in treating FHM (Black, DF. 2006).

3.4.4 Chloride Ion Channelopathies With Molecular Mechanism

3.4.4.1 Myotonia Congenita

Myotonia congenita is a congenital myopathy that can be characterized by muscle stiffness and their inability to relax after contraction which affects the bodily movements. The myotonic attacks may last from seconds to minutes depending on the severity of disease that could range from slightly uncomfortable to complete disability. Cold, sudden pitched sound can trigger the attacks and can affect various body parts for instance hands, legs, shoulders, hips, face, feet, tongue and eyelids (Colding-Jorgensen, E. 2005). Myotonia congenita can be classified into two forms of congenital myopathy based on the inheritance pattern and severity of symptoms, for instance Thomsen's diseases and Becker's disease that have been inherited in an autosomal dominant and autosomal recessive pattern respectively. It has been reported that mutations in the same ClCN1 gene have been responsible for the occurrence of both Thomsen's and Becker's disease (Zhang *et al.*, 1996; Sun *et al.*, 2001; Pusch, M. 2002). Mutated ClCN1 gene disrupts ClC-1 chloride channel thereby interrupting the normal process of repolarization. Electrophysiological studies in a recessive CLCN1 patient suggested that prolonged repolarization takes place due to reduced inflow of chloride ions into the skeletal muscles thereby causing prolonged muscle contraction in the myotonial patients (Lucchiari *et al.*,2013). No perfect cure has been reported till now but patients usually learn to adopt preventive measures and can use medicines, for instance mexiletine, quinine, procanimide, tegretol, and phenytoin to relieve the symptoms (Fazio, B. 1988; Trip *et al.*, 2006).

3.4.4.2 Thomsen's Disease- it is an autosomal dominant muscle disorder characterized by muscle stiffness and relaxation inability after contraction (Sun *et al.*,2001). It was first identified by Thomsen in his own family and he himself was also suffering from the same thus named as Thomsen's disease. It exhibits the above mentioned symptoms but with less severity than Becker's disease with carbamazepine as a potential drug

used for relieving against Thomsen's disease (Lyons *et al.*, 2010; Savitha *et al.*, 2006).

3.4.4.3 Becker's Disease-It is a more common and severe form of myotonia congenita with autosomal recessive pattern of inheritance (Harper and Johnston., 1972) that follow the above mentioned molecular mechanism. Along with the later onset most of the affected persons feel transient muscle weakness during muscle exertion or after rest and have been encountered by the muscular hypertrophy especially in the region of legs and buttocks while symptoms can be relieved with the use of sodium channel blocker (Kuhn, E. 1993).

The above discussed diseases have been defined at either molecular or genetic levels **[Figure 5]** that include mutations in the ion channel present in the tissues such as skeletal muscle, brain and heart (Koopmann *et al.*, 2009) that have been summarized in **Table 5**. However, disease phenotypes are directly related to the extent of functional deficit in ion channels.

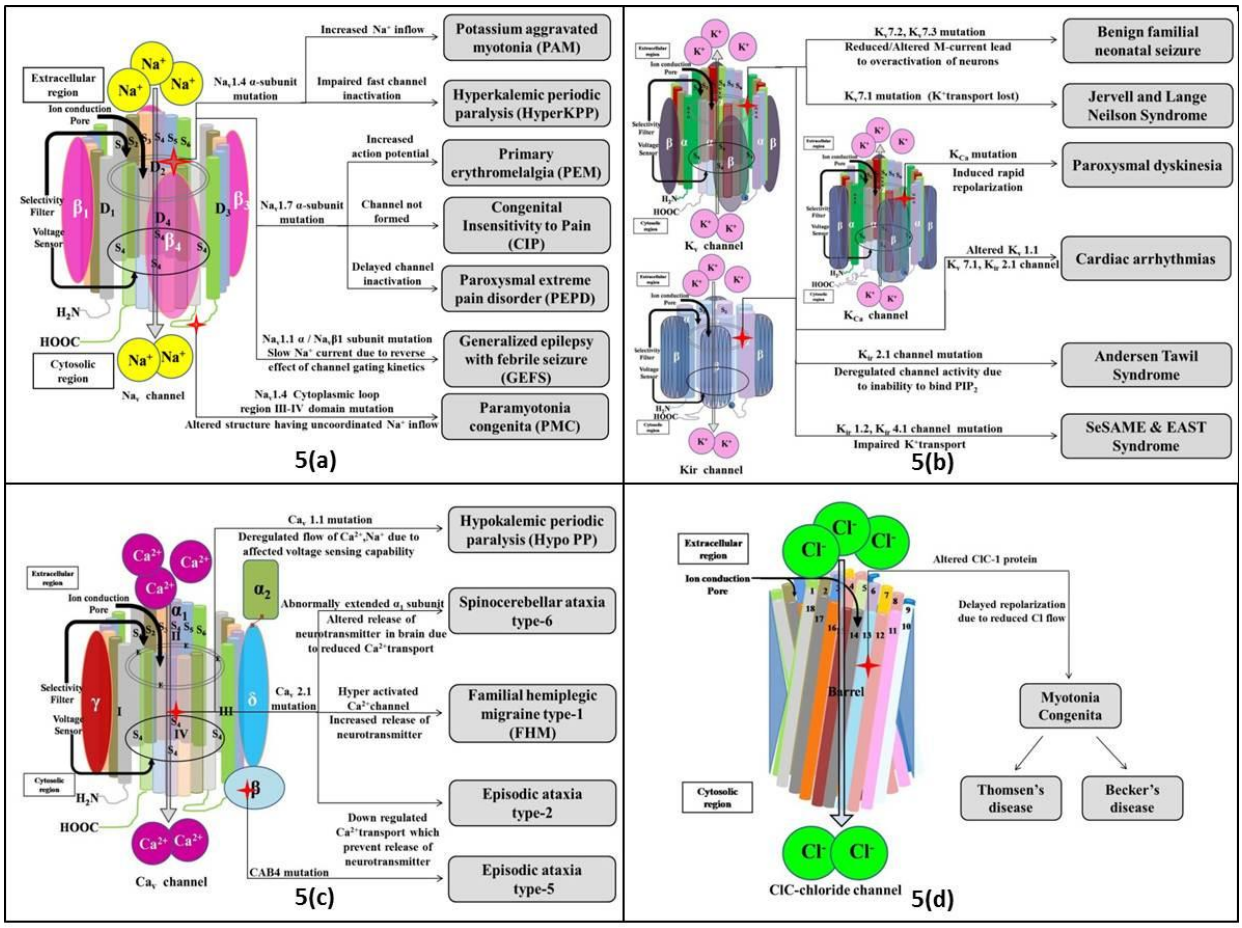


Figure 5: (a) Sodium ion channelopathies: Mutated Nav1.4 alpha subunit has lead to Potassium aggravated myotonia (PAM) and Hyperkalemic periodic paralysis while mutations in Na_v 1.7 alpha subunit have caused Primary erythro-melalgia (PEM), congenital insensitivity to pain (CIP) and Paroxysmal extreme pain disorder (PEPD). Moreover, $Na_v1.1$ alpha and Na_v beta subunit mutations known to cause Generalized epilepsy with febrile seizure whereas Na_v 1.4 cytoplasmic loop mutations between domain III and IV have caused Paramyotonia congenita (PMC). **(b) Potassium ion channelopathies:** Mutated $K_v7.2$ and 7.3 channels resulted into benign familial neonatal seizure and mutated K_v 7.1 channel lead to Jervell and Lange Nielsen syndrome. Moreover K_{ca} channel mutation is responsible for Paroxysmal dyskinesia and

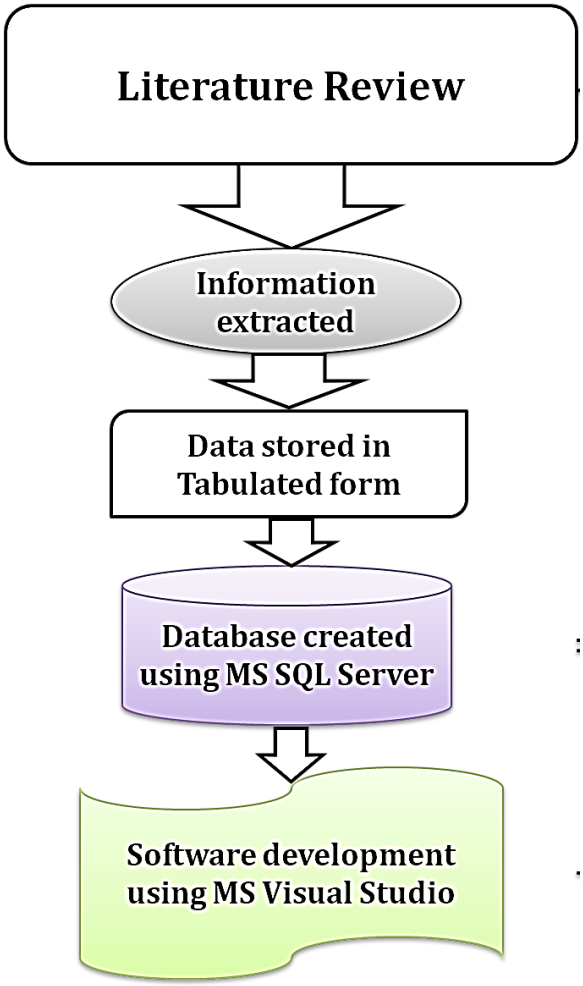
altered K_v 1.1, K_v 7.1 and K_{ir} 2.1 channel cause Cardiac arrhythmias. Apart from this K_{ir} 2.1 channel mutation lead to Andersen Tawil Syndrome while K_{ir} 1.2 and K_{ir} 4.1 channel mutations lead to SeSAME and EAST syndrome. **(c) Calcium ion channelopathies:** Mutated $Ca_v1.1$ channel is known to cause Hypokalemic periodic paralysis (Hypo PP) and $Ca_v2.1$ channel mutations lead to Spino cerebellar ataxia type-6, Familial hemiplegic migraine type-1 (FHM-1) and episodic ataxia type-2 while Calcium channel beta subunit CAB4 mutations caused Episodic ataxia type-5. **(d) Chloride ion channelopathies:** Mutated CLC-1 channel cause Myotonia congenita that can be categorized into Thomsen's and Becker's disease based on symptoms.

Tissue affected	Ion channels	Gene	Channel subunit	Disease caused	Symptoms	Mechanism	References
Skeletal muscle	Cl Channel	ClCN1	ClC-1 (Chloride channel protein 1)	Myotonia congenita	Muscle stiffness, inability to relax after contraction	Mutated channel either become nonfunctional or open at a more depolarized potential thus losses chloride conductance thereby increasing the time taken for repolarization due to which muscle hyper excitability takes place thus causing myotonia	(Lee *et al.*, 2013) (Duran *et al.*, 2010) (Lossin and George., 2008) (Koch *et al.*, 1992)
				Thomsen's disease	Proximal muscle weakness, myalgia and muscular hypertrophy	Mutated channels results in moderate decrease in chloride conduction and following the above mentioned molecular mechanism it causes mild symptoms	(Wu *et al.*, 2002) (Kubisch *et al.*, 1998) (Koch et al. 1992)
				Becker's disease	Muscle hypertrophy and distal muscle weakness	Mutated channel proteins have not get expressed to the optimum level thereby causing great reduction in chloride conduction and thus causing myotonia by following the above mentioned mechanism	(Graves and Hanna., 2005) (Wu *et al.*, 2002) (Kubisch *et al.*, 1998)
	Na_v Channel	SCN4A	$Na_v1.4$ (Sodium channel protein type 4 subunit alpha)	Potassium-aggravated myotonia (PAM)	Sustained muscle tension and inability to relax muscle	The altered channels up regulate the sodium ion influx into the skeletal muscles thereby triggering prolonged muscle contractions due to one or more of the following reasons for instance reduced fast channel inactivation, enhanced recovery rate from fast inactivation, slowed deactivation or hyperpolarizing shift in steady state activation	(Orrell *et al.*, 1998) (Cummins and Bendahhou., 2009) (Vicart *et al.*, 2005)
				Para-myotonia congenita (PMC)	Cold sensitive myotonia and episodic muscular weakness	Mutated sodium channels exhibit slowed inactivation and faster recovery from inactivation thus causing hyper excitability of muscles (myotonia) and sometimes inexcitability that causes episodic weakness in muscles	(Heine *et al.*, 1993) (McClatchey *et al.*,1992) (Ptacek *et al.*, 1992) (Tamaoaka, A. 2003) (Vicart et al., 2005)
				Hyper-kalemic periodic paralysis (hyperKPP)	Extreme muscle weakness and increased level of potassium during attacks	Due to altered anchoring site of fast inactivation particle in mutated channel, persistent sodium current takes place that causes depolarization of the cell thereby inactivating other normal sodium channels due to the absence of action potential	(Bendahhou *et al.*, 2002) (Ptacek *et al.*, 1991) (Rojas *et al.*, 1991)
	Na_v & Ca_v Channel	SCN4A and CACNA1S	$Na_V1.4$ (Sodium channel protein type 4 subunit alpha) CaV1.1 (Voltage-dependent L-type calcium channel subunit alpha-1S)	Hypo-kalemic periodic paralysis (hypoKPP)	Extreme muscle weakness associated with low potassium level in serum	Mutated sodium and calcium channels are responsible for abnormal gating pore currents i.e. shift in the resting membrane potential to a more depolarized second stable state (paradoxical depolarization). Moreover due to their affected voltage sensing capability deregulated flow of Ca2+ and Na+ ions into the muscles take place thereby causing reduced contractibility of muscles and ultimately muscle weakness	(Sokolov *et al.*, 2010) (Jurkat-Rott *et al.*, 2009) (Sokolov *et al.*, 2007) (Bulman *et al.*, 1999) (Jurkat- Rott *et al.*, 1994) (Ptacek *et al.*, 1994)
Peri-pheral Nerve	Na_v Channel	SCN9A	$Na_v1.7$ (Sodium channel protein type 9 subunit alpha)	Primary erythro-melalgia	Burning pain, flushing and swelling of the feet, hands and sometimes other areas	Mutated sodium channels exhibit hyperpolarizing shift toward activation and slowed inactivation kinetics that makes opening of channel easier and prolonged. Thus increased inflow of sodium ions enhances transmission of pain signals, leading to the signs and symptoms of erythro-melalgia	(Dib-Hajj *et al.*, 2005) (Waxman *et al.*, 2005a & b) (Estacion *et al.*, 2011)
				Paroxysmal extreme pain disorder (PEPD)	Burning pain and flushing in the sub-mandibular, ocular, and rectal areas	Mutated sodium channels that expressed in nociceptive dorsal root ganglion and sympathetic ganglion neurons cannot be able to close as quickly as usual leading to prolonged transmission of pain signals. Moreover we can say that gain of function mutations result in increased action potential duration and therefore more synaptic transmission thus causing heightened pain perception	(Fertleman *et al.*, 2007) (Lampert *et al.*, 2010)
				Congenital in-sensitivity to pain (CIP)	Complete loss of pain sensation	Mutated channel exhibit complete functional loss that leads to an inability to form action potentials and therefore loss of pain sensation	(Cox *et al.*, 2006) (Goldberg *et al.*, 2007)

Central Nervous System	K_v, Ca_v, Channel and Glutamate transporter	KCNA1, CACNA1A CACNB4 SLC1A3	K_v1.1 (Potassium channel sub-family A member 1) Cav2.1 (Calcium channel Subunit alpha), Sodium-dependent glutamate/ aspartate transporter1	Episodic ataxias	Problems with movements, poor coordination and balance	These genes alter the transport of ions and glutamate into the brain that causes certain neurons to become overexcited and disrupts normal communication between these cells. Moreover it also results in decreased current often due to protein instability. Furthermore potassium channels are vital in down stroke of action potential and its mutation cause prolonged action potential and altered excitability of different neuronal population	(Jen *et al.*, 2007) (Wan *et al.*, 2005) (Browne *et al.*, 1994) (Zerr *et al.*, 1998)
	K_v Channel	KCNMA1	K_{ca} (Potassium large conductance calcium-activated channel, subfamily M, alpha member 1)	Paroxysmal dyskinesias	Sudden, unpredictable disabling attacks of involuntary movements	Mutated channels formed due to altered KCNMA1 gene promotes excitability of neurons by inducing rapid repolarization of action potential that allows neurons to conduct at a faster rate thereby causing recurrent attacks	(Lee and Cui., *2009)* *(Du* et al., *2005)*
		KCNQ2 KCNQ3	K_v7.2 & K_v7.3 (Potassium voltage-gated channel subfamily KQT member 2 & 3)	Benign familial neonatal seizures (BFNS)	Recurrent seizures in new-born babies, muscle rigidity, convulsions, and loss of consciousness	Channels coded by KCNQ2 and KCNQ3 genes transmit M-currents that ensure normal shutting of active neuron, while mutated genes result in reduced or altered M-current which cause excessive excitability of neurons that results in the development of seizures in brain	(Biervert *et al.*,1998) (Singh *et al.*, 1998) (Charlier et al., 1998) (Castaldo *et al.*, 2002)
	Na_v Channel	SCN1A SCN1B	Na_V1.1 (Sodium channel type 1 subunit alpha)	Generalized epilepsy with febrile seizures (GEFS)	It is characterized by a long term recurring seizures.	However, it arises from many causes that include metabolic brain disorders, abnormalities of cortical development, brain trauma or structural lesions of the brain (brain tumours), while mutated channel is also one of the prominent factor that causes over excitation of neurons and ultimately epilepsy with seizures	(Catterall *et al.*, 2010) (Tan *et al.*, 2012) (Xu *et al.*, 2012)
	Ca_v & Na_v Channels	CACNA1A ATP1A2 SCN1A	Ca_v2.1 (Calcium channel Subunit alpha) ATP1A2 (ATPase subunit alpha-2) Na_V1.1 (Sodium channel type 1 subunit alpha)	Familial hemiplegic migraine (FHM)	Intense, throbbing pain in one area of the head, often accompanied by nausea, vomiting, and extreme sensitivity to light and sound.	Altered channels formed by these mutated genes disrupt the normal release and re uptake of certain neurotransmitters in brain that result in the alteration of signaling between neurons thereby causing hemiplegic migraine. Moreover these mutated genes cause three different types of Familial hemiplegic migraine that are CACNA1A mutations cause FHM1, ATP1A2 mutations cause FHM2 and SCN1A mutations cause FHM3	(Pietrobon, D. 2010), (Cestele et al., 2008) (Gritz et al., 2013) (Pelzer et al., 2013) (Ducros et al., 2001)
	Ca_v Channel	CACNA1A	Ca_v2.1 (Calcium channel Subunit alpha)	Spino-cerebellar ataxia type-6 (SCA6)	Progressive pure cerebellar ataxia, poor coordination of hands, speech, and eye movements, Impaired speech, Patient progressively lose physical control	Expansion of CAG repeats were found at the 3' region that generates poly glutamine tract thereby producing abnormally extended α1 subunit of calcium channel that abnormally aggregate calcium channel protein thereby affecting neurotransmitter's release in the brain eventually causing death of neurons	(Graves and Hanna., 2005) (Denier *et al.*, 1999) (Rajakulendran *et al.*, 2010) (Zhuchenko., *et al.*, 1997)
Heart	K_v and Na_v Channels	KCNE1 KCNE2 KCNH2 KCNQ1 KCNJ2 SCN5A	K_v (Voltage gated potassium channel subfamily E member 1 &2, subfamily H member 2, subfamily Q member 1, subfamily J member 2), Na_v (Sodium channel protein type 5 subunit alpha)	Cardiac arrhythmia	Dizziness, palpitations, syncope, deficits in executive function and abstract reasoning, even cause death	Irregularities in heart rhythm via mutated channel is reported due to triggered activity, which involves impulse initiation due to the membrane potential oscillations occurring just after an action potential that results in abnormal transmission of electrical impulse in the heart cell thereby causing aberrant cardiac rhythm	(Schimpf *et al.*, 2013) (Campuzano et al., 2010)
	Inward Rectifier Potassium (Kir) Channel	KCNJ2	Kir2.1 (Inwardly rectifying potassium channel subfamily J member 2)	Andersen-Tawil syndrome (ATS)	Muscle weakness (periodic paralysis), changes in heart rhythm (arrhythmia) and developmental abnormalities like widespread eyes, cleft palate and syndactyly of the toes.	Mutations in the KCNJ2 gene alter the usual structure and function of potassium channels that prevent the channels from being inserted correctly into the cell membrane. Moreover it also prevent binding of PIP2 that disrupt the flow of potassium ions in skeletal and cardiac muscles thus leading to periodic paralysis and irregular heart rhythm	(Plaster *et al.*, 2001) (Tristani-Firouzi *et al.*, 2010) (Donaldson *et al.*, 2004) (Tristani-Firouzi *et al.*, 2002)
		KCNJ10	Kir4.1 (ATP-dependent inwardly rectifying potassium channel Kir4.1)	SeSAME syndrome and EAST syndrome	Characterized by generalized seizures with onset in infancy, delayed psychomotor development, ataxia, sensorineural hearing loss, hypokalemia, metabolic alkalosis and hypomagnesaemia.	Mutated inward rectifier potassium channel disrupts the potassium buffering action of glial cells in the brain and disturbs the homeostasis of potassium ions in various organs like inner ear, retina and kidney thus exhibiting the symptoms of SeSAME	(Bockenhauer *et al.*, 2009) (Scholl *et al.*,2009)
	K_v Channel	KCNE1 & KCNQ1	K_v (Potassium voltage gated channel subfamily E member 1,subfamily Q member1)	Jervell and Lange-Nielson syndrome (J-LN)	Cardiac arrhythmia concomitant with deafness	Mutated genes affect potassium channel structure and function thereby preventing the assembly of normal channels. These changes disrupt the flow of potassium ions in the inner ear and in cardiac muscle, leading to hearing loss and an irregular heart rhythm	(Schulze-Bahr *et al.*, 1997) (Schwartz *et al.*, 2006) (Wang *et al.*, 2002)

Table 5: Channelopathies associated with various ion channels and their physiology

METHODOLOGY



Schematic overview of software development

4.1 Database creation using SQL Server Management Studio 2005:

Two databases have been created using the valuable information extracted from the literature review.

a. Neurological Channelopedia
It is a database containing the repositories of ion channel subtypes of sodium, potassium, calcium and chloride channels and their characteristics.

b. Neurological Channelopathies
It is a database containing the repositories of ion channels that have been associated with neurological diseases.

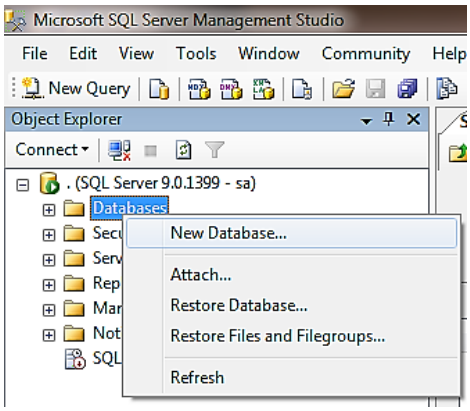
4.1.1 Steps for Database creation:

a. Install SQL-2005 setup into your system
b. Start SQL Server Management studio 2005
c. Connect to Server
    i. Enter Server name '.'

ii. Login ‘sa’

iii. Password ‘1234’

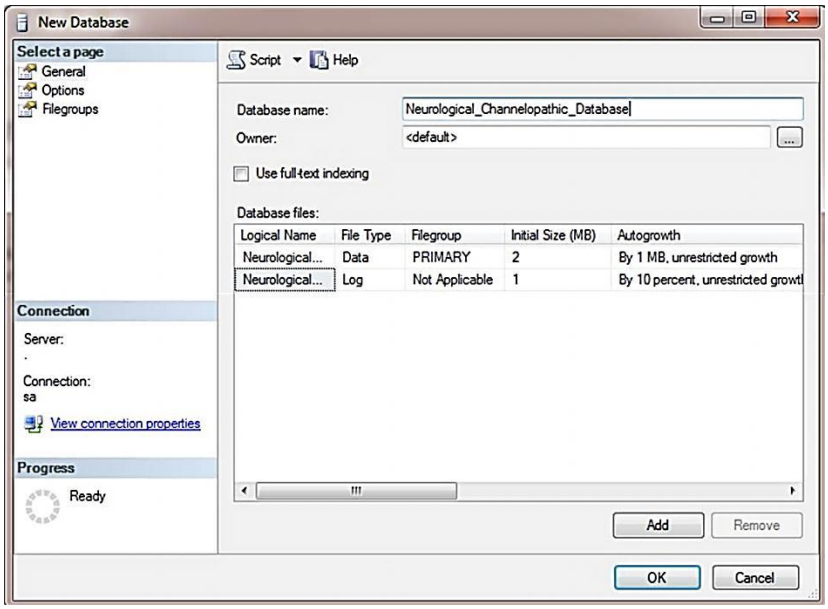
d. Creation of Database



Right click on 'Database'

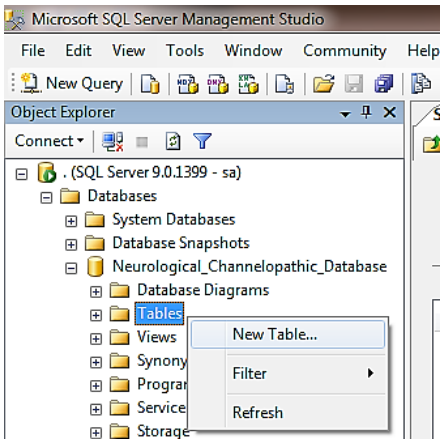
Click on ‘New Database’

Enter 'Database name'



e. Creation of Tables

Table Channelopathy

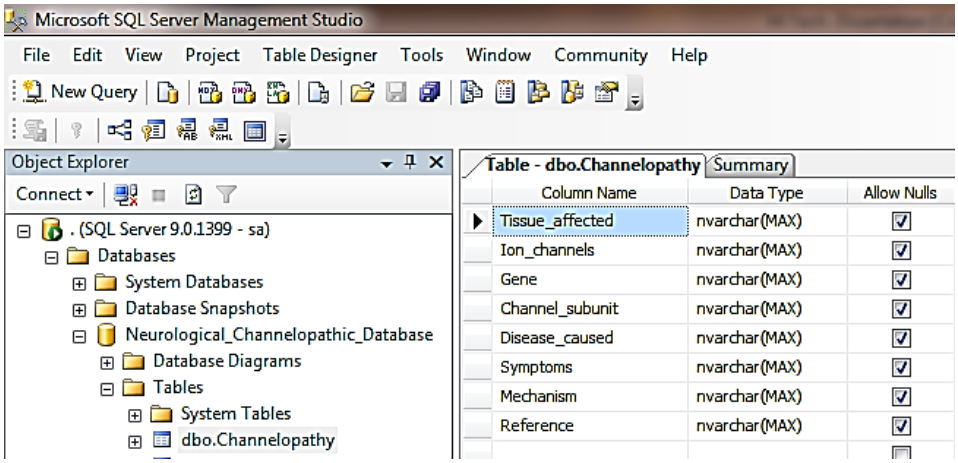


Right click on 'Tables'

Click on 'New Table'

Enter 'Column Name' and 'Data Type'

Rename Table 'Channelopathy'



Enter Data into Rows

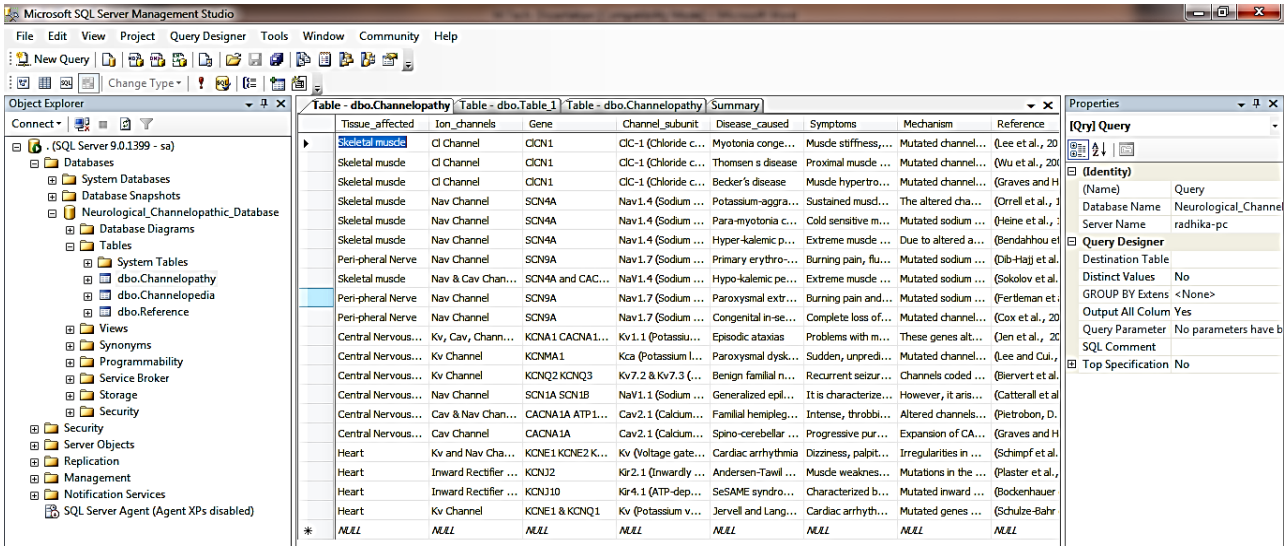
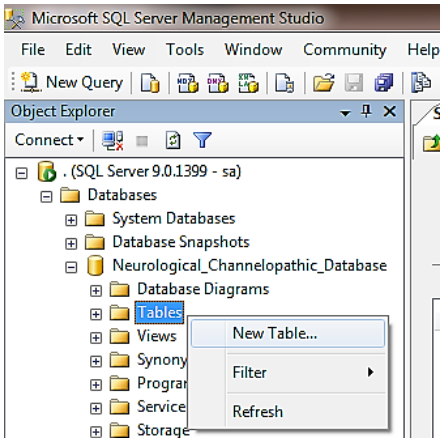


Table Channelopedia

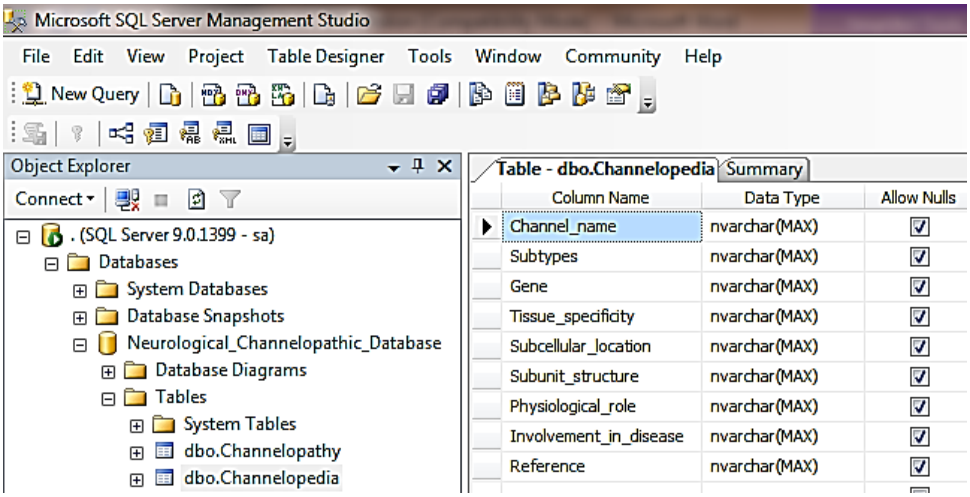


Right click on 'Tables'

Click on 'New Table'

Enter 'Column Name' and 'Data Type'

Rename Table 'Channelopedia'



Enter Data into Rows

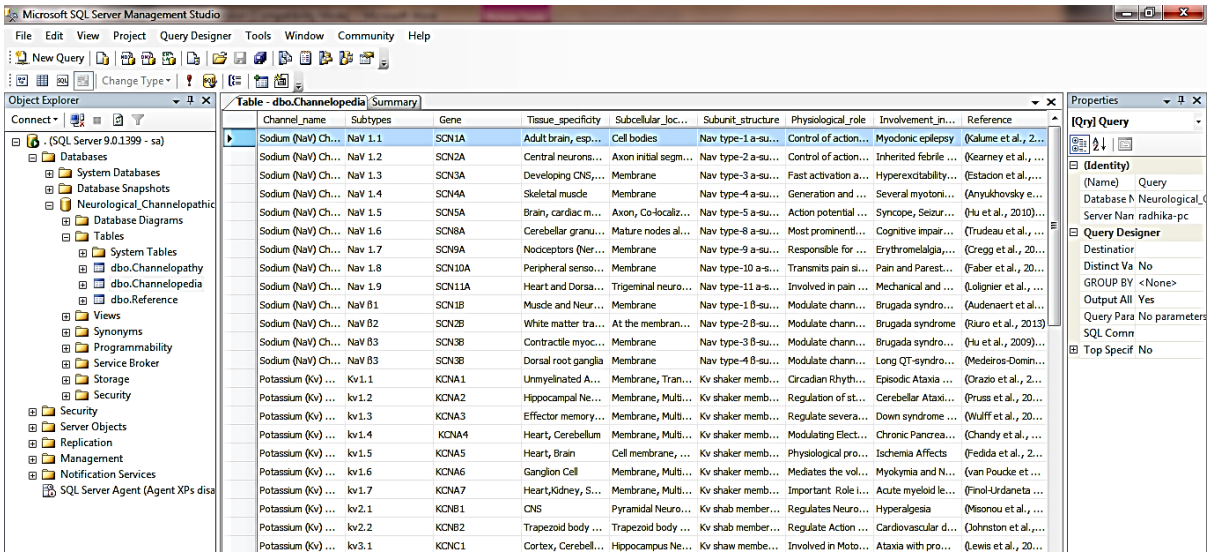
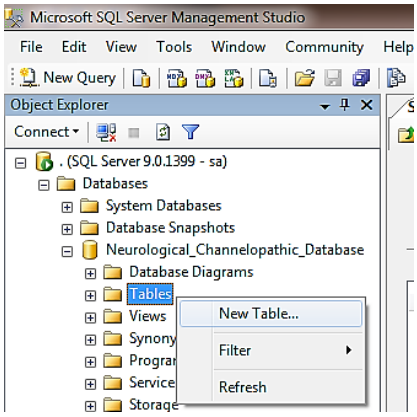


Table Reference

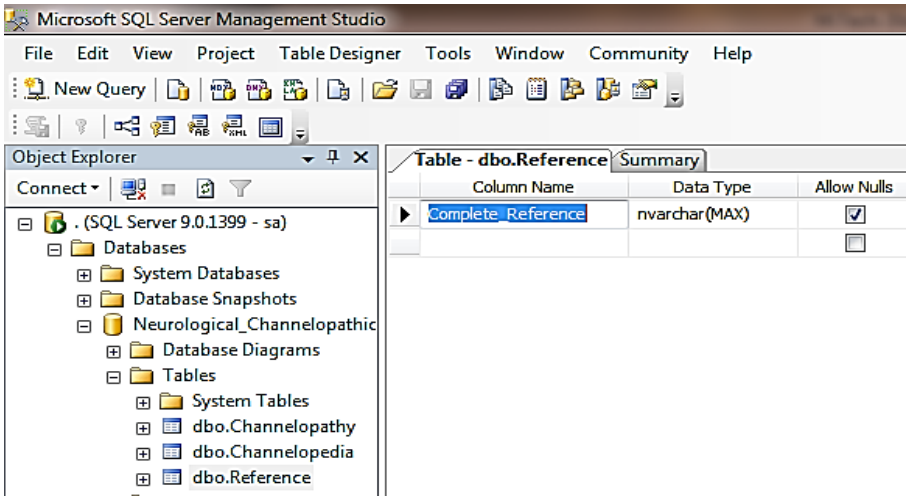


Right click on 'Tables'

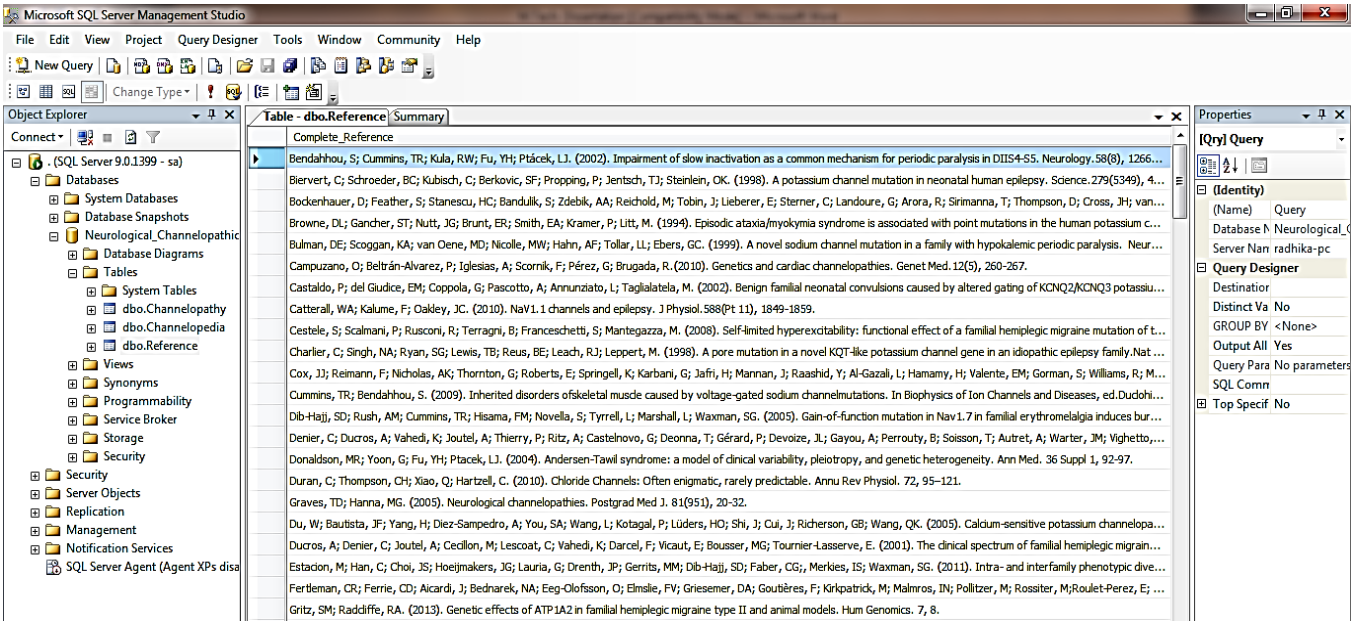
Click on 'New Table'

Enter 'Column Name' and 'Data Type'

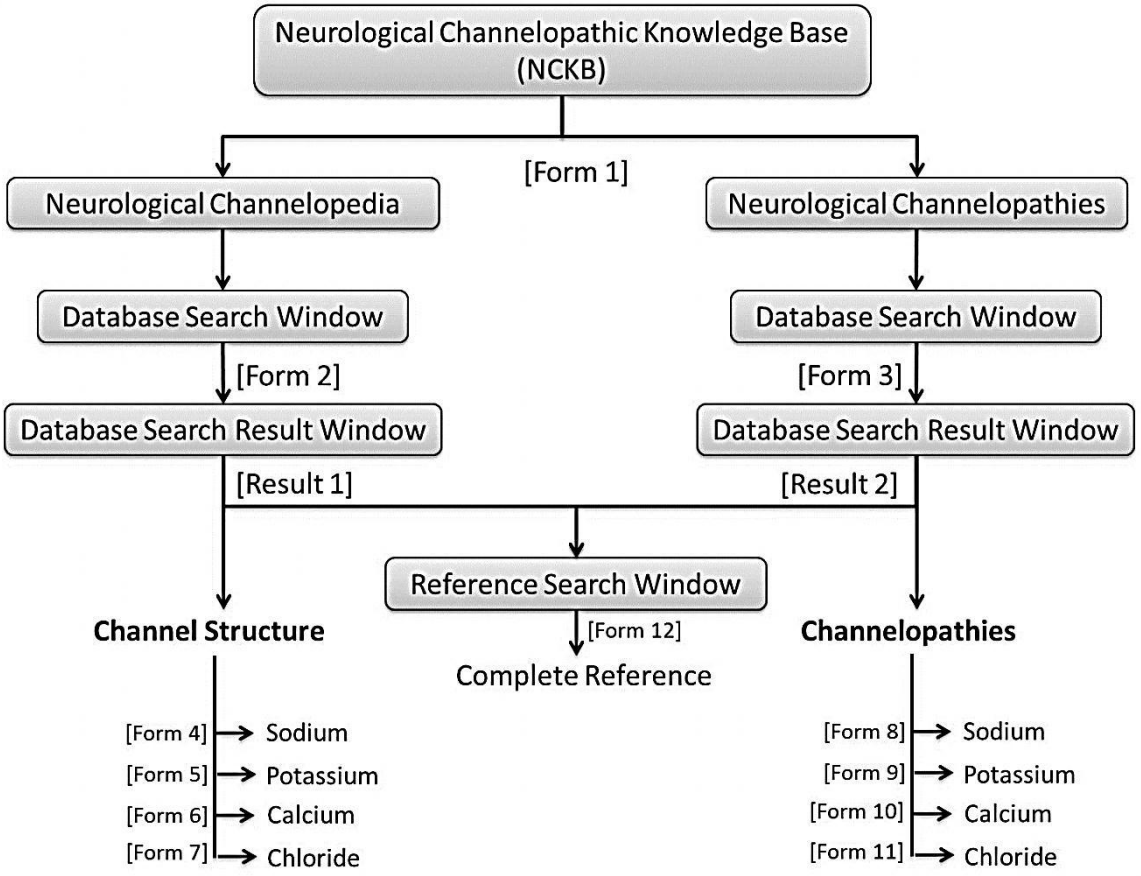
Rename Table 'Reference'



Enter Data into Rows



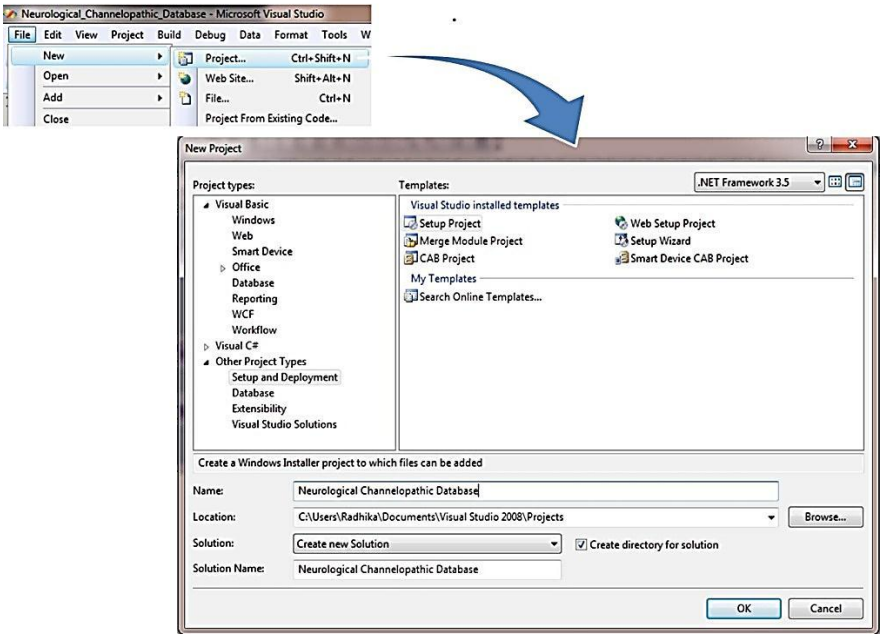
4.2 Software development using Microsoft Visual Studio 2008:



Neurological Channelopathic Knowledge Base (NCKB) software design layout

4.2.1 Building a project using Microsoft Visual Studio 2008

Software has been developed with the use of Microsoft Visual Studio 2008. Software development requires the creation of a project, designing the Forms and finally coding into the forms. File→New→Project

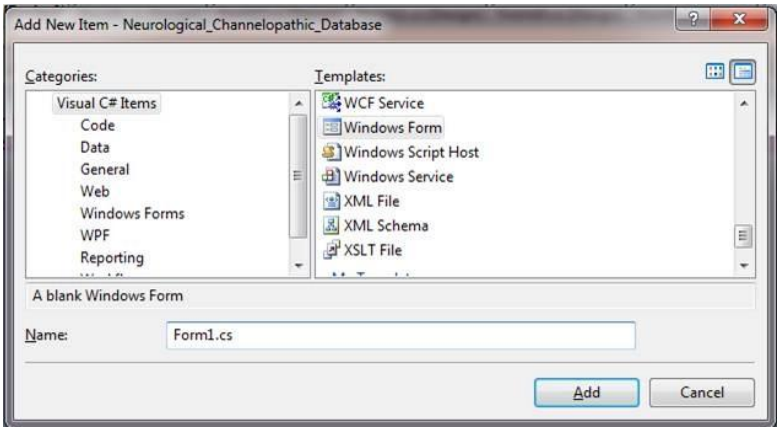


4.2.2 Designing of Window Forms:

All Window forms have been loaded from 'Project' menu tab.

Project→Add Window Form

And Click on 'Add'



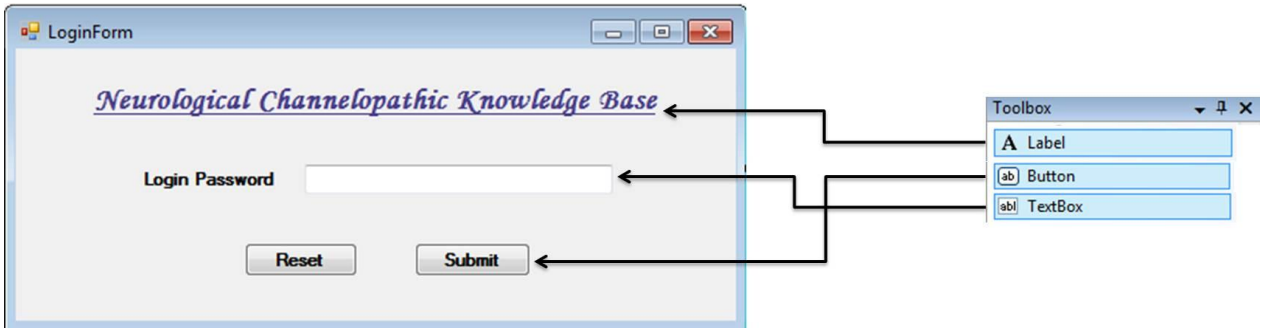
Window forms have been designed using tools from Toolbox under tab 'All Window Forms'.

View→Toolbox Ctrl+Alt+X

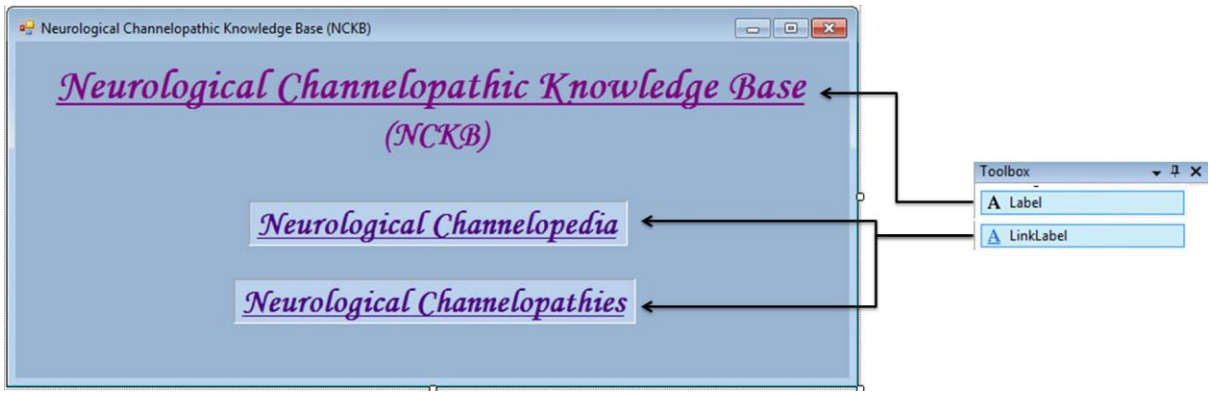
And Properties have been modified with the use of tools available in 'Properties Window'.

View→Properties Window F4

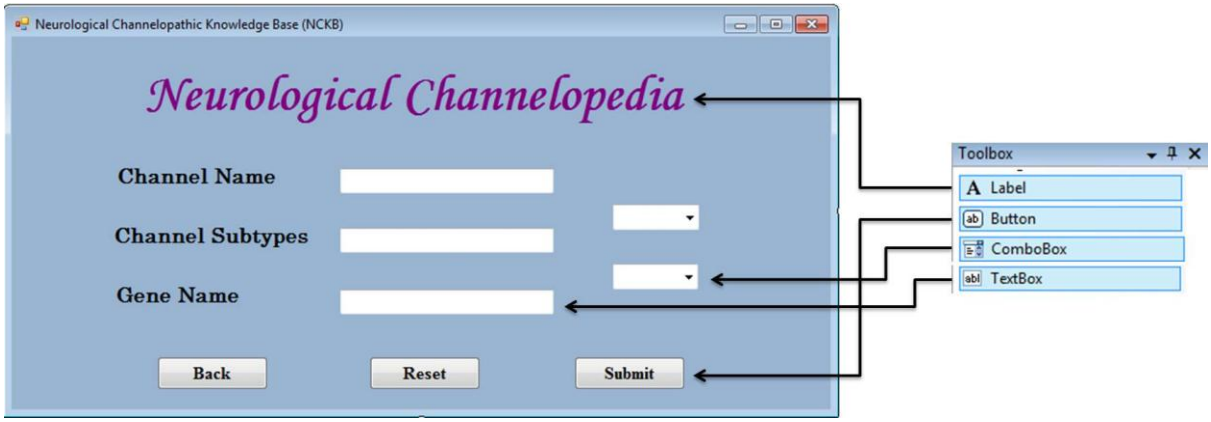
LoginForm Design:



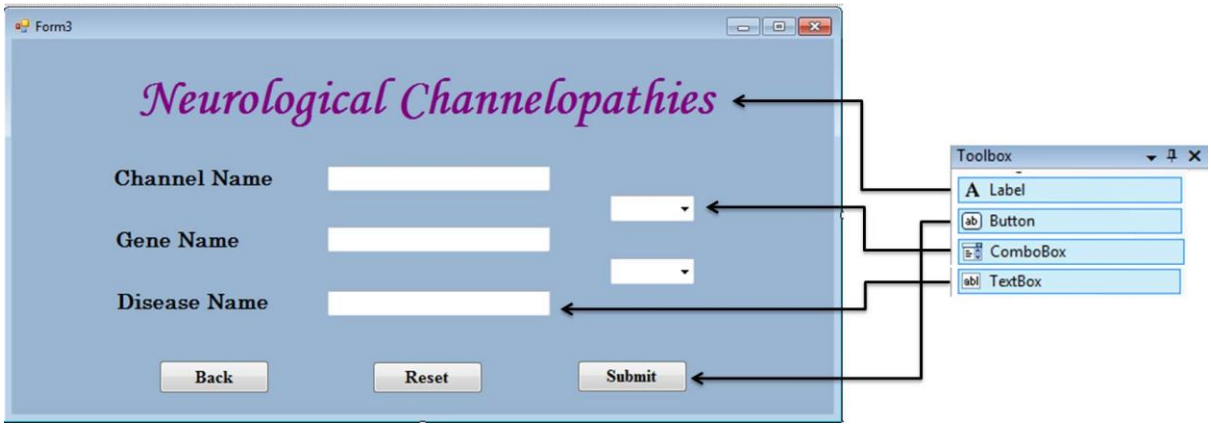
Form1 Design:



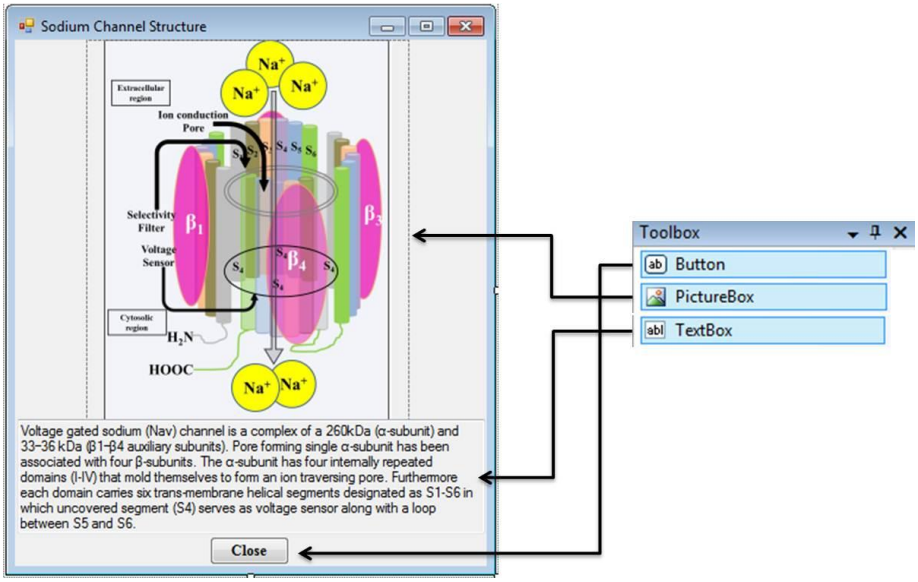
Form 2 Design:



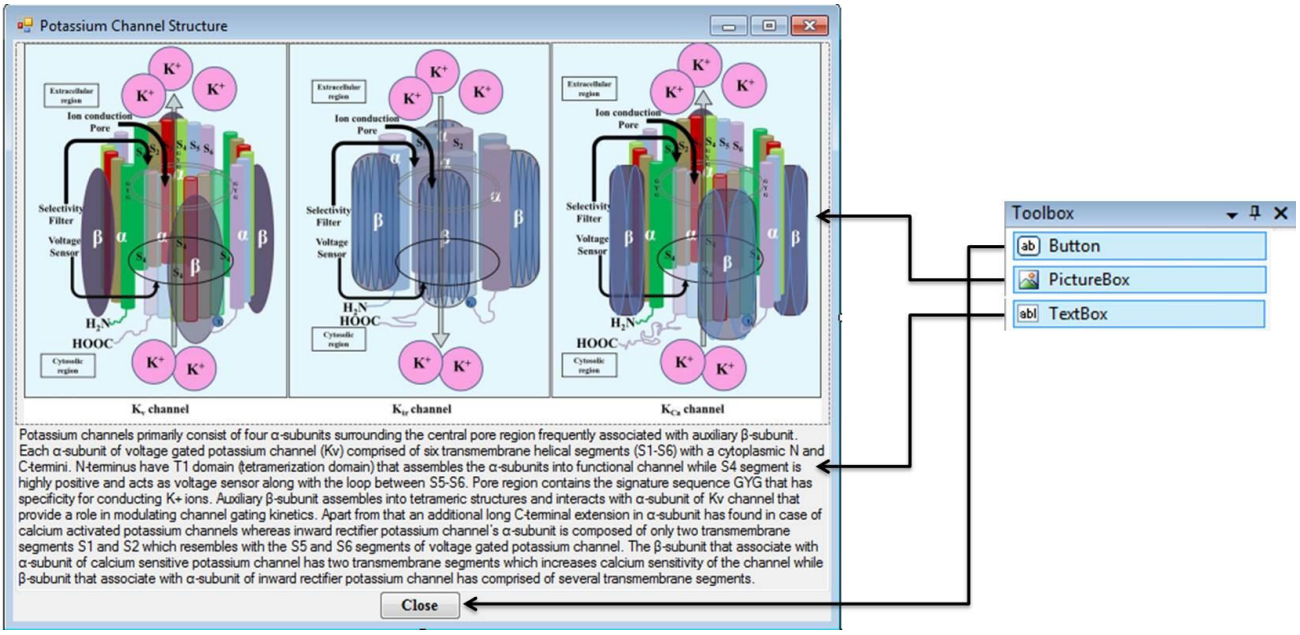
Form 3 Design:



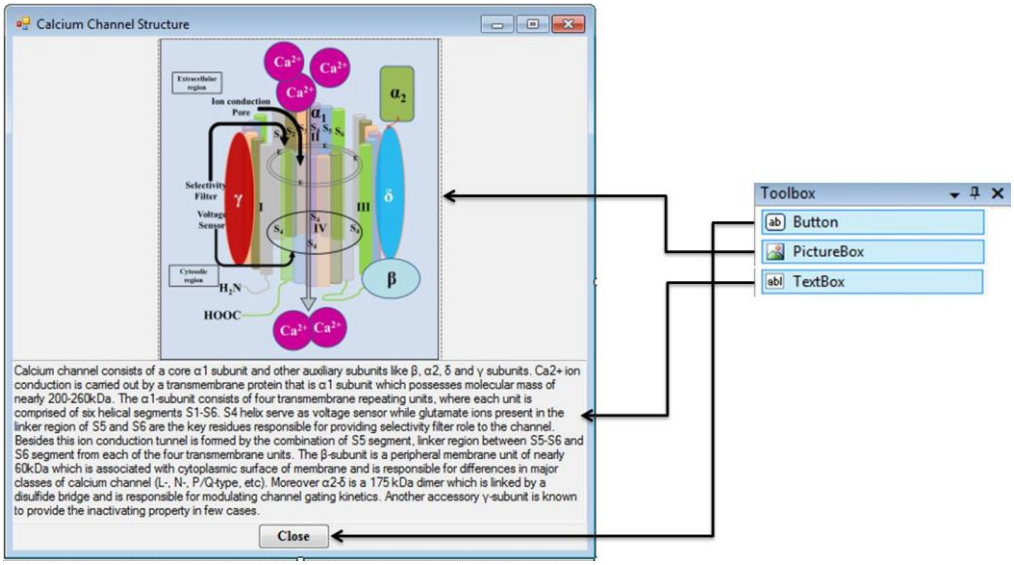
Form 4 Design:



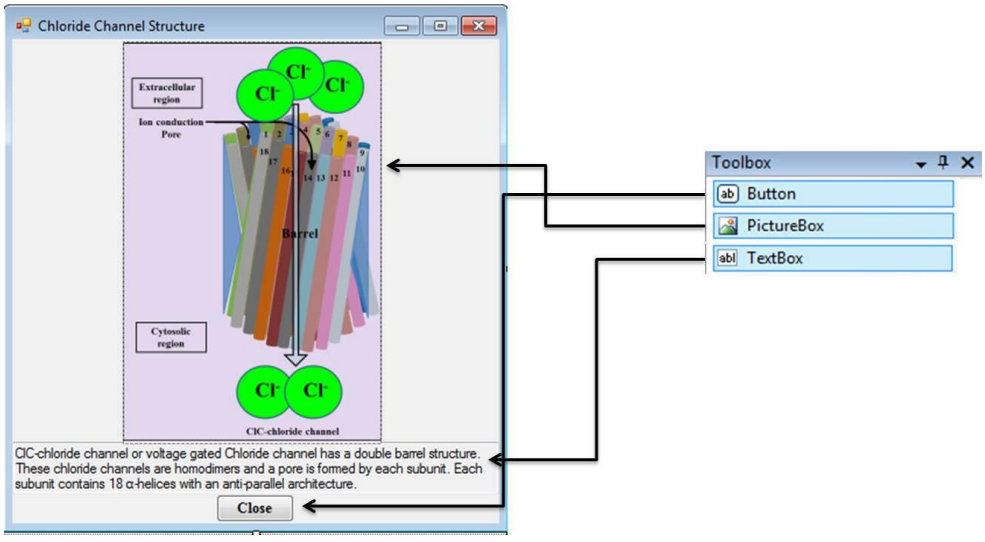
Form 5 Design



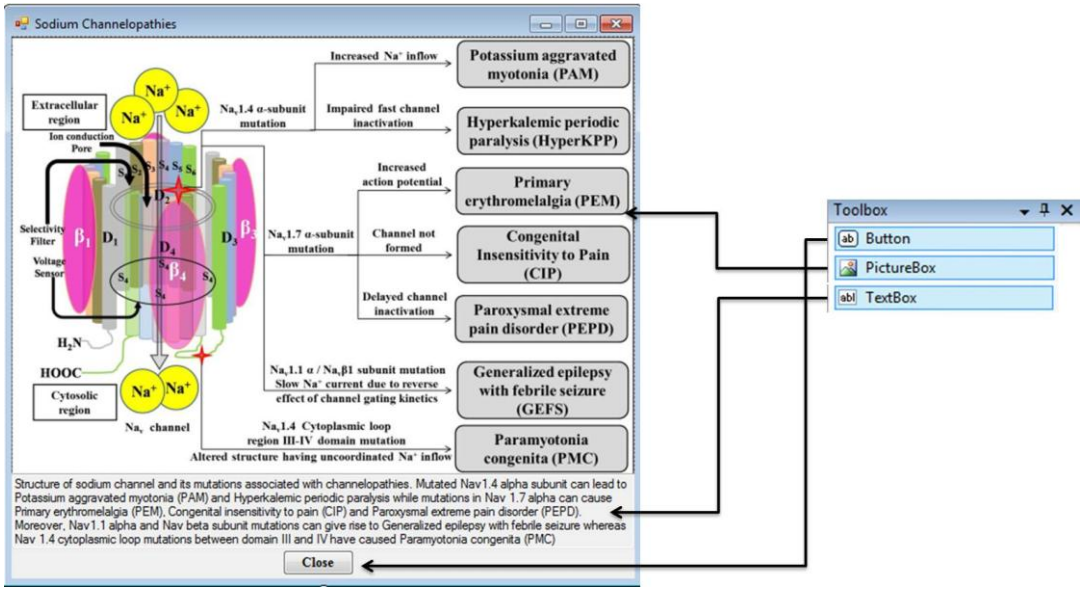
Form 6 Design:



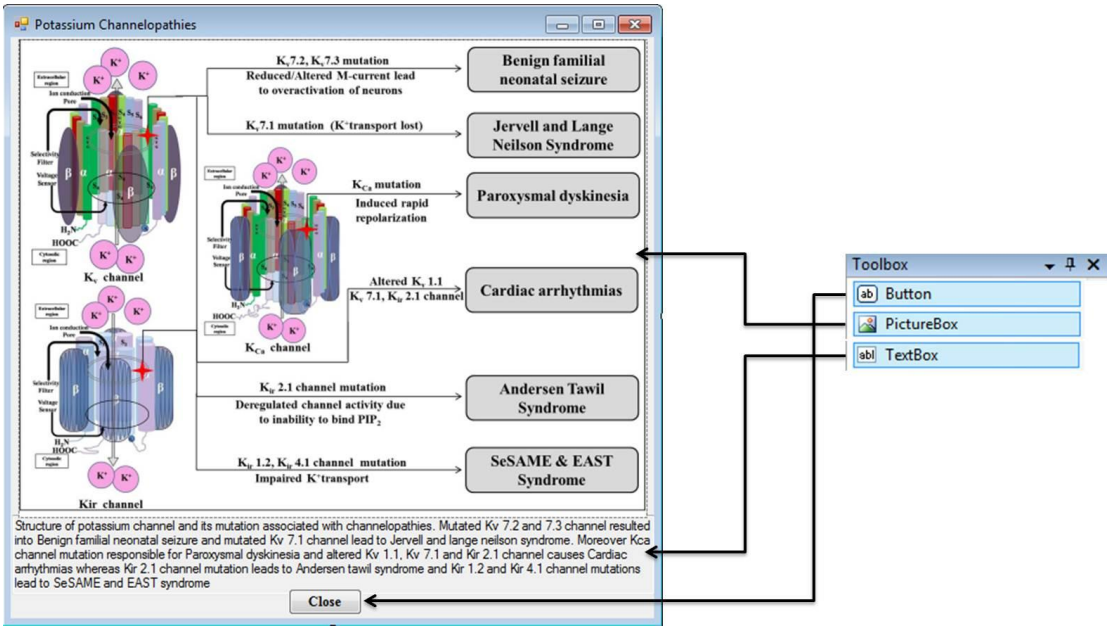
Form 7 Design:



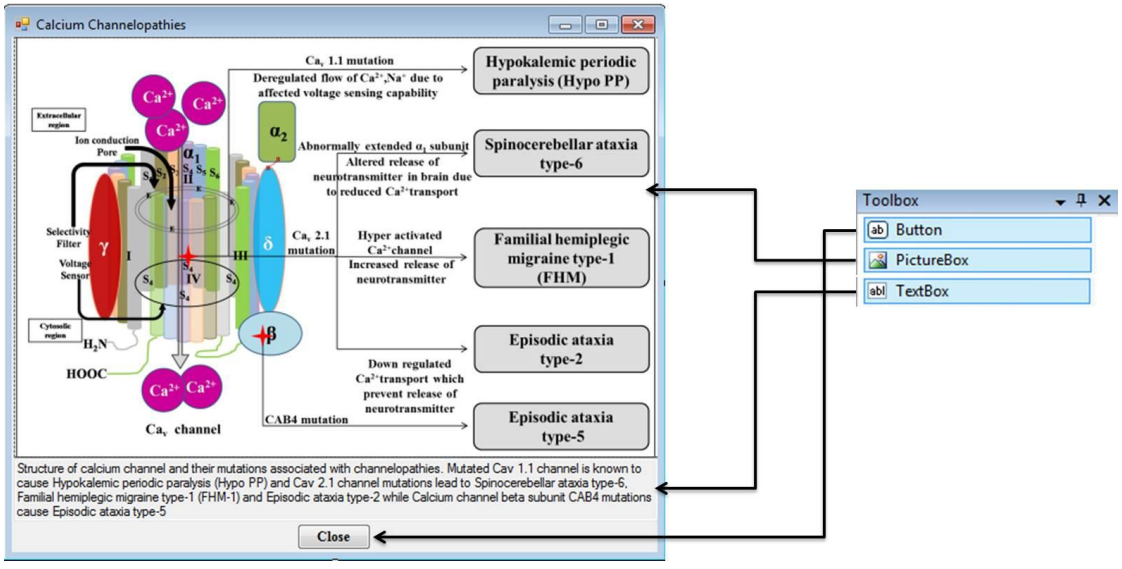
Form 8 Design:



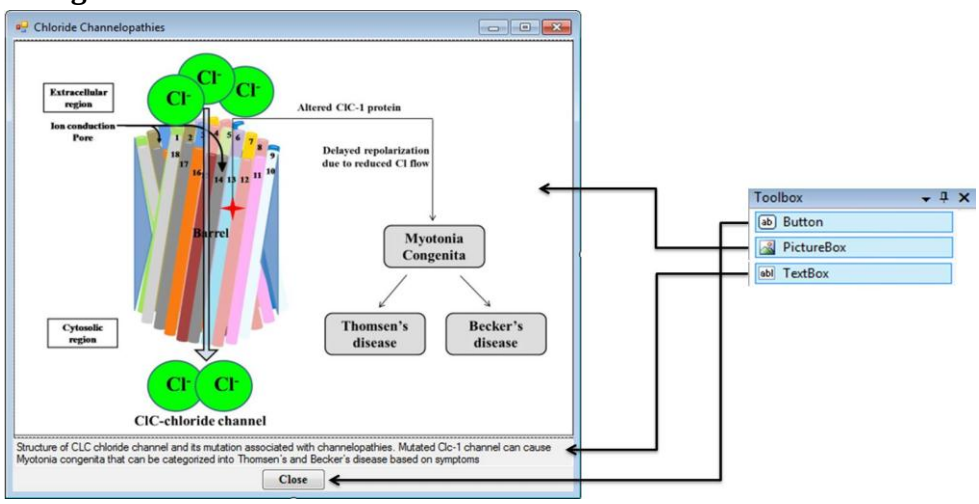
Form 9 Design:



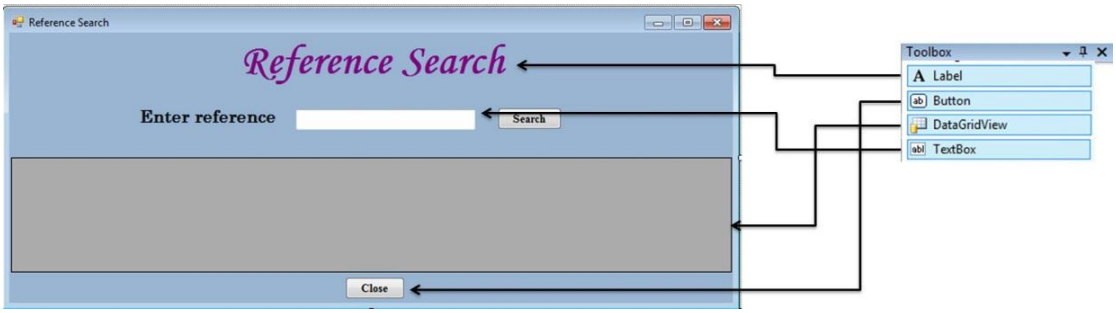
Form 10 Design:



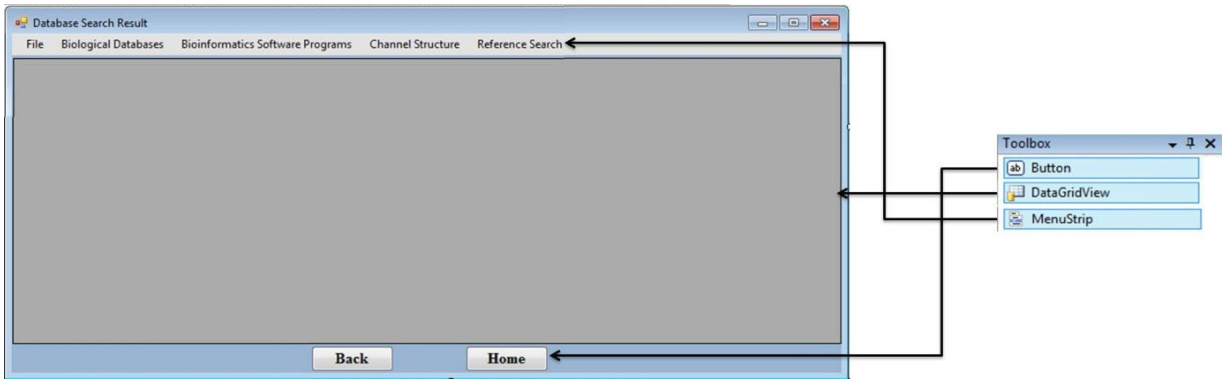
Form 11 Design:



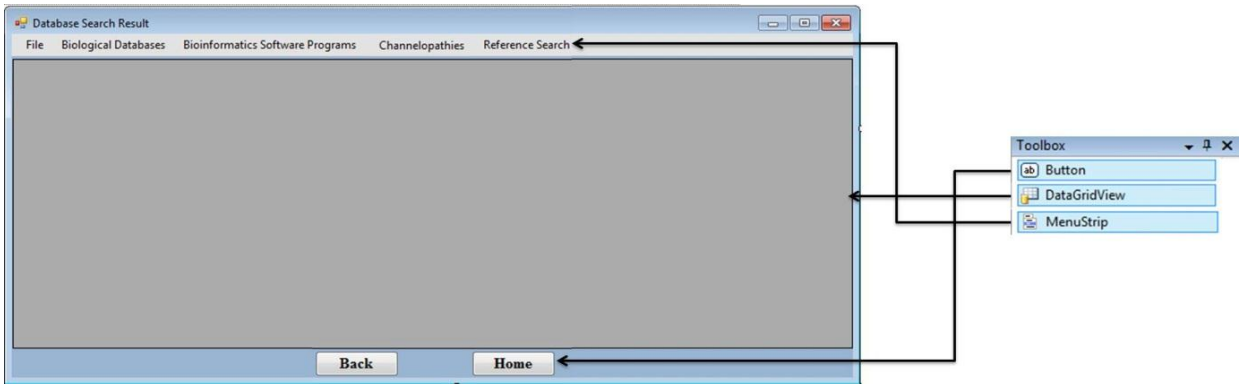
Form 12 Design:



Result1 Design:



Result 2 Design:



4.2.3 Form Coding using C#:

Form coding is essential for assigning functions to the tools used in the designing of forms. Forms have been coded using C# (C-sharp) language.

- ✓ **Steps to write code:**
  - i. Select the tool that has to be coded.
  - ii. Select tab 'Events' from properties.
  - iii. Double click on the desired event.
  - iv. Write the desired code in the space provided.

OR

  - i. Double click on the tool that has to be assign code.
  - ii. Then Form.cs file would be open.
  - iii. Write the desired code in the space provided.

- ✓ **Template of Form.cs file:**
  - i. Include library files: - These are the files that contain the definitions of various syntax code used for coding.
  - ii. Declare Namespace: - It is a name of Database that has been created.
  - iii. Declaration of Public Class: - It is a public partial class that has been applicable for the whole form.
  - iv. Declaration of Events applied to the tools used and coding inside the space provided.

LoginForm.cs Code

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class LoginForm : Form
  {
   public LoginForm()
   {
     InitializeComponent();
     textBox1.Focus();
   }

   private void button2_Click(object sender, EventArgs e)
   {
     textBox1.Text = "";
     textBox1.Focus();
   }

   private void button1_Click(object sender, EventArgs e)
   {
     if (textBox1.Text == "KnowledgeBase4U")
     {
       Form1 f1 = new Form1();
       f1.Show();
       this.Hide();
     }
     else
     {
       MessageBox.Show("Please enter correct password!");
```

```
        textBox1.Clear();
        textBox1.Focus();
      }
    }
  }
}
```

Form1.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Form1 : Form
  {
    public Form1()
    {
      InitializeComponent();
    }

    private void linkLabel1_LinkClicked(object sender, LinkLabelLinkClickedEventArgs e)
    {
      Form2 f2 = new Form2();
      f2.Show();
      this.Hide();
    }

    private void linkLabel2_LinkClicked(object sender, LinkLabelLinkClickedEventArgs e)
    {
      Form3 f3 = new Form3();
      f3.Show();
      this.Hide();
    }
  }
}
```

Form 2.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Form2 : Form
  {
    public Form2()
    {
      InitializeComponent();
    }

    private void Form2_Load(object sender, EventArgs e)
    {
      ChannelName.Text = "Enter Text Here";
      ChannelName.ForeColor = Color.LightSlateGray;
      Subtypes.Text = "Enter Text Here";
      Subtypes.ForeColor = Color.LightSlateGray;
      Gene.Text = "Enter Text Here";
      Gene.ForeColor = Color.LightSlateGray;
      cmb1.Text = "Select";
      cmb1.ForeColor = Color.LightSlateGray;
      cmb2.Text = "Select";
      cmb2.ForeColor = Color.LightSlateGray;
      ChannelName.Focus();
```

```
    }

    private void button1_Click(object sender, EventArgs e)
    {
       Form1 f1 = new Form1();
       f1.Show();
       this.Hide();
    }

    private void button2_Click(object sender, EventArgs e)
    {
       ChannelName.Text = "Enter Text Here";
       ChannelName.ForeColor = Color.LightSlateGray;
       Subtypes.Text = "Enter Text Here";
       Subtypes.ForeColor = Color.LightSlateGray;
       Gene.Text = "Enter Text Here";
       Gene.ForeColor = Color.LightSlateGray;
       cmb1.Text = "Select";
       cmb1.ForeColor = Color.LightSlateGray;
       cmb2.Text = "Select";
       cmb2.ForeColor = Color.LightSlateGray;
       ChannelName.Focus();
     }

     private void button3_Click(object sender, EventArgs e)
     {
       Result1 r1 = new Result1(ChannelName.Text, Subtypes.Text, Gene.Text, cmb1.Text,
cmb2.Text);
       r1.Show();
       this.Hide();
     }

     private void ChannelName_Click(object sender, EventArgs e)
     {
       ChannelName.ForeColor = Color.Black;
     }

     private void ChannelName_Enter(object sender, EventArgs e)
     {
       ChannelName.Clear();
     }

     private void ChannelName_TextChanged(object sender, EventArgs e)
     {
       ChannelName.ForeColor = Color.Black;
     }

     private void ChannelName_Leave(object sender, EventArgs e)
     {
       if(ChannelName.Text == "")
       {
         ChannelName.Text = "Enter Text Here";
         ChannelName.ForeColor = Color.LightSlateGray;
       }
     }

     private void Subtypes_Click(object sender, EventArgs e)
     {
       Subtypes.ForeColor = Color.Black;
     }

     private void Subtypes_Enter(object sender, EventArgs e)
     {
       Subtypes.Clear();
     }

     private void Subtypes_TextChanged(object sender, EventArgs e)
     {
       Subtypes.ForeColor = Color.Black;
     }

     private void Subtypes_Leave(object sender, EventArgs e)
     {
       if (Subtypes.Text == "")
       {
         Subtypes.Text = "Enter Text Here";
         Subtypes.ForeColor = Color.LightSlateGray;
       }
     }
```

```
private void Gene_Click(object sender, EventArgs e)
{
  Gene.ForeColor = Color.Black;
}

private void Gene_Enter(object sender, EventArgs e)
{
  Gene.Clear();
}

private void Gene_TextChanged(object sender, EventArgs e)
{
  Gene.ForeColor = Color.Black;
}

private void Gene_Leave(object sender, EventArgs e)
{
  if (Gene.Text == "")
  {
    Gene.Text = "Enter Text Here";
    Gene.ForeColor = Color.LightSlateGray;
  }
}

private void cmb1_Leave(object sender, EventArgs e)
{
  if (cmb1.Text == "AND")
  {
    cmb1.Text = "AND";
    cmb1.ForeColor = Color.Black;
  }
  else if (cmb1.Text == " OR")
  {
    cmb1.Text = " OR";
    cmb1.ForeColor = Color.Black;
  }
  else if (cmb1.Text == "NOT")
  {
    cmb1.Text = "NOT";
    cmb1.ForeColor = Color.Black;
  }
  else if (cmb1.Text == "Select")
  {
    cmb1.Text = "Select";
    cmb1.ForeColor = Color.LightSlateGray;
  }
  else
  {
    cmb1.Text = "Select";
    cmb1.ForeColor = Color.LightSlateGray;
  }
}

private void cmb2_Leave(object sender, EventArgs e)
{
  if (cmb2.Text == "AND")
  {
    cmb2.Text = "AND";
    cmb2.ForeColor = Color.Black;
  }
  else if (cmb2.Text == " OR")
  {
    cmb2.Text = " OR";
    cmb2.ForeColor = Color.Black;
  }
  else if (cmb2.Text == "NOT")
  {
    cmb2.Text = "NOT";
    cmb2.ForeColor = Color.Black;
  }
  else if (cmb2.Text == "Select")
  {
    cmb2.Text = "Select";
    cmb2.ForeColor = Color.LightSlateGray;
  }
  else
  {
    cmb2.Text = "Select";
```

```
            cmb2.ForeColor = Color.LightSlateGray;
        }
      }
    }
}
```

Form 3.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
   public partial class Form3 : Form
   {
     public Form3()
     {
       InitializeComponent();
     }
     private void Form3_Load(object sender, EventArgs e)
     {
       ChannelName.Text = "Enter Text Here";
       ChannelName.ForeColor = Color.LightSlateGray;
       GeneName.Text = "Enter Text Here";
       GeneName.ForeColor = Color.LightSlateGray;
       DiseaseName.Text = "Enter Text Here";
       DiseaseName.ForeColor = Color.LightSlateGray;
       cmb1.Text = "Select";
       cmb1.ForeColor = Color.LightSlateGray;
       cmb2.Text = "Select";
       cmb2.ForeColor = Color.LightSlateGray;
       ChannelName.Focus();
     }

     private void button1_Click_1(object sender, EventArgs e)
     {
       Form1 f1 = new Form1();
       f1.Show();
       this.Hide();
     }

     private void button2_Click_1(object sender, EventArgs e)
     {
       ChannelName.Text = "Enter Text Here";
       ChannelName.ForeColor = Color.LightSlateGray;
       GeneName.Text = "Enter Text Here";
       GeneName.ForeColor = Color.LightSlateGray;
       DiseaseName.Text = "Enter Text Here";
       DiseaseName.ForeColor = Color.LightSlateGray;
       cmb1.Text = "Select";
       cmb1.ForeColor = Color.LightSlateGray;
       cmb2.Text = "Select";
       cmb2.ForeColor = Color.LightSlateGray;
       ChannelName.Focus();
     }

     private void button3_Click_1(object sender, EventArgs e)
     {
       Result2 r2 = new Result2(ChannelName.Text, GeneName.Text, DiseaseName.Text, cmb1.Text,
cmb2.Text);
       r2.Show();
       this.Hide();
     }

     private void ChannelName_Click(object sender, EventArgs e)
     {
       ChannelName.ForeColor = Color.Black;
     }

     private void ChannelName_Enter(object sender, EventArgs e)
     {
       ChannelName.Clear();
```

```
}

private void ChannelName_TextChanged(object sender, EventArgs e)
{
  ChannelName.ForeColor = Color.Black;
}

private void ChannelName_Leave(object sender, EventArgs e)
{
  if (ChannelName.Text == "")
  {
    ChannelName.Text = "Enter Text Here";
    ChannelName.ForeColor = Color.LightSlateGray;
  }
}

private void GeneName_Click(object sender, EventArgs e)
{
  GeneName.ForeColor = Color.Black;
}

private void GeneName_Enter(object sender, EventArgs e)
{
  GeneName.Clear();
}

private void GeneName_TextChanged(object sender, EventArgs e)
{
  GeneName.ForeColor = Color.Black;
}

private void GeneName_Leave(object sender, EventArgs e)
{
  if (GeneName.Text == "")
  {
    GeneName.Text = "Enter Text Here";
    GeneName.ForeColor = Color.LightSlateGray;
  }
}

private void DiseaseName_Click(object sender, EventArgs e)
{
  DiseaseName.ForeColor = Color.Black;
}

private void DiseaseName_Enter(object sender, EventArgs e)
{
  DiseaseName.Clear();
}

private void DiseaseName_TextChanged(object sender, EventArgs e)
{
  DiseaseName.ForeColor = Color.Black;
}

private void DiseaseName_Leave(object sender, EventArgs e)
{
  if (DiseaseName.Text == "")
  {
    DiseaseName.Text = "Enter Text Here";
    DiseaseName.ForeColor = Color.LightSlateGray;
  }
}

private void cmb1_Leave(object sender, EventArgs e)
{
  if (cmb1.Text == "AND")
  {
    cmb1.Text = "AND";
    cmb1.ForeColor = Color.Black;
  }
  else if (cmb1.Text == " OR")
  {
    cmb1.Text = " OR";
    cmb1.ForeColor = Color.Black;
  }
  else if (cmb1.Text == "NOT")
  {
    cmb1.Text = "NOT";
```

```
          cmb1.ForeColor = Color.Black;
        }
        else if (cmb1.Text == "Select")
        {
         cmb1.Text = "Select";
         cmb1.ForeColor = Color.LightSlateGray;
        }
        else
        {
          cmb1.Text = "Select";
          cmb1.ForeColor = Color.LightSlateGray;
        }
      }

      private void cmb2_Leave(object sender, EventArgs e)
      {
        if (cmb2.Text == "AND")
        {
          cmb2.Text = "AND";
          cmb2.ForeColor = Color.Black;
        }
        else if (cmb2.Text == " OR")
        {
          cmb2.Text = " OR";
          cmb2.ForeColor = Color.Black;
        }
        else if (cmb2.Text == "NOT")
        {
          cmb2.Text = "NOT";
          cmb2.ForeColor = Color.Black;
        }
        else if (cmb2.Text == "Select")
        {
          cmb2.Text = "Select";
          cmb2.ForeColor = Color.LightSlateGray;
        }
        else
        {
          cmb2.Text = "Select";
          cmb2.ForeColor = Color.LightSlateGray;
        }
     }
   }
}
```

Form 4.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Form4 : Form
  {
    public Form4()
    {
      InitializeComponent();
    }

    private void button2_Click(object sender, EventArgs e)
    {
      this.Close();
    }
  }
}
```

Form 5.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
```

```
using System.Data;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Form5 : Form
  {
    public Form5()
    {
      InitializeComponent();
    }

    private void button2_Click(object sender, EventArgs e)
    {
      this.Close();
    }
  }
}
```

Form 6.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Form6 : Form
  {
    public Form6()
    {
      InitializeComponent();
    }
    private void button2_Click(object sender, EventArgs e)
    {
      this.Close();
    }
  }
}
```

Form 7.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Form7 : Form
  {
    public Form7()
    {
      InitializeComponent();
    }
    private void button2_Click(object sender, EventArgs e)
    {
      this.Close();
    }
  }
}
```

Form 8.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Form8 : Form
  {
    public Form8()
    {
      InitializeComponent();
    }

    private void button2_Click(object sender, EventArgs e)
    {
      this.Close();
    }
  }
}
```

Form 9.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Form9 : Form
  {
    public Form9()
    {
      InitializeComponent();
    }

    private void button2_Click(object sender, EventArgs e)
    {
      this.Close();
    }
  }
}
```

Form 10.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Form10 : Form
  {
    public Form10()
    {
      InitializeComponent();
    }

    private void button2_Click(object sender, EventArgs e)
```

```
    {
      this.Close();
    }
  }
}
```

Form 11.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Form11 : Form
  {
    public Form11()
    {
      InitializeComponent();
    }

    private void button2_Click(object sender, EventArgs e)
    {
      this.Close();
    }
  }
}
```

Form 12.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Data.SqlClient;
using System.Diagnostics;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Form12 : Form
  {
    string sql;
    SqlConnection con;
    DataSet ds;
    SqlDataAdapter sda;

    public Form12()
    {
      InitializeComponent();
    }

    private void Form12_Load(object sender, EventArgs e)
    {
      textBox1.Text = "Enter Text Here";
      textBox1.ForeColor = Color.LightSlateGray;
    }

    private void button2_Click(object sender, EventArgs e)
    {
      this.Hide();
    }

    private void textBox1_Click(object sender, EventArgs e)
    {
      textBox1.ForeColor = Color.Black;
    }
```

```
    private void textBox1_Enter(object sender, EventArgs e)
    {
      textBox1.Clear();
    }

    private void textBox1_TextChanged(object sender, EventArgs e)
    {
      textBox1.ForeColor = Color.Black;
    }

    private void textBox1_Leave(object sender, EventArgs e)
    {
      if (textBox1.Text == "")
      {
        textBox1.Text = "Enter Text Here";
        textBox1.ForeColor = Color.LightSlateGray;
      }
    }

    private void button1_Click(object sender, EventArgs e)
    {
      try
      {
        string connectionString = "Data Source=.;Initial
Catalog=Neurological_Channelopathic_Database;User ID=sa;Password=1234";

        if (textBox1.Text == "Enter Text Here")
        {
          MessageBox.Show("Please enter or paste 'reference search text' and then click on
'Search' button");
          this.Close();
          Form12 f12 = new Form12();
          f12.Show();
        }
        else
        {
          sql = "SELECT * FROM Reference WHERE Complete_Reference LIKE '%" + textBox1.Text +
"%'";
        }

      con = new SqlConnection(connectionString);
      sda = new SqlDataAdapter(sql, con);
      ds = new DataSet();
      con.Open();
      sda.Fill(ds, "Reference");
      con.Close();
      dataGridView1.DataSource = ds;
      dataGridView1.DataMember = "Reference";
    }
    catch (Exception es)
    {
      Console.WriteLine(es.ToString());
    }
  }
 }
}
```

Result1.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Data.SqlClient;
using System.Diagnostics;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Result1 : Form
  {
    string sql;
    SqlConnection con;
    DataSet ds;
```

```
    SqlDataAdapter sda;

    private string cname = string.Empty;
    private string stype = string.Empty;
    private string gname = string.Empty;
    private string slct1 = string.Empty;
    private string slct2 = string.Empty;

  public Result1(string _cname, string _stype, string _gname, string _slct1, string _slct2)
  {
    InitializeComponent();
    this.cname = _cname;
    this.stype = _stype;
    this.gname = _gname;
    this.slct1 = _slct1;
    this.slct2 = _slct2;
  }

  private void Result_Load(object sender, EventArgs e)
  {
    try
    {
      string connectionString = "Data Source=.;Initial
Catalog=Neurological_Channelopathic_Database;User ID=sa;Password=1234";

      if (cname != "Enter Text Here")
      {
       if (stype != "Enter Text Here")
       {
        if (gname != "Enter Text Here")
        {
         if (slct1 == "AND")
         {
          if (slct2 == "AND")
          {
            sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' AND
Subtypes Like '%" + stype + "%' AND Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == " OR")
          {
            sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' AND
Subtypes Like '%" + stype + "%' OR Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == "NOT")
          {
            sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' AND
Subtypes Like '%" + stype + "%' AND NOT Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == "Select")
          {
            sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' AND
Subtypes Like '%" + stype + "%'";
          }
         }
         else if (slct1 == " OR")
         {
          if (slct2 == "AND")
          {
            sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' OR
Subtypes Like '%" + stype + "%' AND Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == " OR")
          {
            sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' OR
Subtypes Like '%" + stype + "%' OR Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == "NOT")
          {
            sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' OR
Subtypes Like '%" + stype + "%' AND NOT Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == "Select")
          {
            sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' OR
Subtypes Like '%" + stype + "%'";
          }
         }
         else if (slct1 == "NOT")
         {
```

```
          if (slct2 == "AND")
          {
            sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' AND
NOT Subtypes Like '%" + stype + "%' AND Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == " OR")
          {
            sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' AND
NOT Subtypes Like '%" + stype + "%' OR Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == "NOT")
          {
            sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' AND
NOT Subtypes Like '%" + stype + "%' AND NOT Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == "Select")
          {
            sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' AND
NOT Subtypes Like '%" + stype + "%'";
          }
         }
         else if (slct1 == "Select")
         {
          if (slct2 == "AND")
          {
            sql = "SELECT * FROM Channelopedia WHERE Subtypes Like '%" + stype + "%' AND
Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == " OR")
          {
            sql = "SELECT * FROM Channelopedia WHERE Subtypes Like '%" + stype + "%' OR
Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == "NOT")
          {
            sql = "SELECT * FROM Channelopedia WHERE Subtypes Like '%" + stype + "%' AND NOT
Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == "Select")
          {
            MessageBox.Show("Error! You have not selected a value from dropdown boxes: Please
search again");
            this.Close();
            Form2 f2 = new Form2();
            f2.Show();
          }
         }
        }
        else if (slct1 == "AND")
        {
          sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' AND
Subtypes Like '%" + stype + "%'";
        }
        else if (slct1 == " OR")
        {
          sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' OR
Subtypes Like '%" + stype + "%'";
        }
        else if (slct1 == "NOT")
        {
          sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%' AND NOT
Subtypes Like '%" + stype + "%'";
        }
        else if (slct1 == "Select")
        {
          MessageBox.Show("Error! You have not selected any option from dropdown box 1: Please
search again");
          this.Close();
          Form2 f2 = new Form2();
          f2.Show();
        }
       }
       else if (gname != "Enter Text Here")
       {
         MessageBox.Show("Please search with a valid search criteria by either using
individual text box search or using multiple text box search with dropdown box option");
         this.Close();
         Form2 f2 = new Form2();
         f2.Show();
```

```
        }
        else
        {
          sql = "SELECT * FROM Channelopedia WHERE Channel_Name Like '%" + cname + "%'";
        }
       }
       else if (stype != "Enter Text Here")
       {
        if (gname != "Enter Text Here")
        {
         if (slct1 == "Select")
         {
          if (slct2 == "AND")
          {
            sql = "SELECT * FROM Channelopedia WHERE Subtypes Like '%" + stype + "%' AND
Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == " OR")
          {
            sql = "SELECT * FROM Channelopedia WHERE Subtypes Like '%" + stype + "%' OR
Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else if (slct2 == "NOT")
          {
            sql = "SELECT * FROM Channelopedia WHERE Subtypes Like '%" + stype + "%' AND NOT
Genes_encoding_subtypes Like '%" + gname + "%'";
          }
          else
          {
            MessageBox.Show("Error! You have not selected any option from dropdown box 2:
Please search again");
            this.Close();
            Form2 f2 = new Form2();
            f2.Show();
          }
         }
         else
         {
           MessageBox.Show("Please search with a valid search criteria by either using
individual text box search or using multiple text box search with dropdown box option");
           this.Close();
           Form2 f2 = new Form2();
           f2.Show();
          }
         }
         else
         {
           sql = "SELECT * FROM Channelopedia WHERE Subtypes Like '%" + stype + "%'";
         }
        }
        else if (gname != "Enter Text Here")
        {
          sql = "SELECT * FROM Channelopedia WHERE Genes_encoding_subtypes Like '%" + gname +
"%'";
        }
        else
        {
          MessageBox.Show("Please search with a valid search criteria by either using
individual text box search or using multiple text box search with dropdown box option");
          this.Close();
          Form2 f2 = new Form2();
          f2.Show();
        }

        con = new SqlConnection(connectionString);
        sda = new SqlDataAdapter(sql, con);
        ds = new DataSet();
        con.Open();
        sda.Fill(ds, "Channelopedia");
        con.Close();
        dataGridView1.DataSource = ds;
        dataGridView1.DataMember = "Channelopedia";
       }
       catch (Exception es)
       {
         Console.WriteLine(es.ToString());
       }
      }
```

```
        private void button1_Click(object sender, EventArgs e)
        {
         Form2 f2 = new Form2();
         f2.Show();
         this.Hide();
        }

        private void button2_Click(object sender, EventArgs e)
        {
          Form1 f1 = new Form1();
          f1.Show();
          this.Hide();
        }

        private void exportToExcelToolStripMenuItem_Click(object sender, EventArgs e)
        {
         if (dataGridView1.Rows.Count > 0)
         {
           Microsoft.Office.Interop.Excel.ApplicationClass XcelApp = new
Microsoft.Office.Interop.Excel.ApplicationClass();
           XcelApp.Application.Workbooks.Add(Type.Missing);

           for (int i = 1; i < dataGridView1.Columns.Count + 1; i++)
           {
             XcelApp.Cells[1, i] = dataGridView1.Columns[i - 1].HeaderText;
           }

           for (int i = 0; i < dataGridView1.Rows.Count; i++)
           {
            for (int j = 0; j < dataGridView1.Columns.Count; j++)
            {
              XcelApp.Cells[i + 2, j + 1] = dataGridView1.Rows[i].Cells[j].Value;
            }
           }

           XcelApp.Columns.AutoFit();
           XcelApp.Visible = true;
          }
         }

         private void closeToolStripMenuItem_Click(object sender, EventArgs e)
         {
           Application.Exit();
         }

         private void genBankToolStripMenuItem_Click(object sender, EventArgs e)
         {
           System.Diagnostics.Process.Start("https://www.ncbi.nlm.nih.gov/genbank//");
         }

         private void eMBLEBIToolStripMenuItem_Click(object sender, EventArgs e)
         {
           System.Diagnostics.Process.Start("http://www.ebi.ac.uk/");
         }

         private void uniProtKBToolStripMenuItem_Click(object sender, EventArgs e)
         {
           System.Diagnostics.Process.Start("http://www.uniprot.org/");
         }

         private void pIRToolStripMenuItem_Click(object sender, EventArgs e)
         {
           System.Diagnostics.Process.Start("http://pir.georgetown.edu/");
         }

         private void genpeptToolStripMenuItem_Click(object sender, EventArgs e)
         {
           System.Diagnostics.Process.Start("http://www.ncbi.nlm.nih.gov/protein");
         }

         private void sCOPToolStripMenuItem_Click(object sender, EventArgs e)
         {
           System.Diagnostics.Process.Start("http://scop.mrc-lmb.cam.ac.uk/scop/index.html");
         }

         private void cATHToolStripMenuItem_Click(object sender, EventArgs e)
         {
           System.Diagnostics.Process.Start("http://www.cathdb.info/");
         }
```

```
private void fSSPToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://protein.hbu.cn/fssp/");
}

private void mMDBToolStripMenuItem_Click(object sender, EventArgs e)
{

  System.Diagnostics.Process.Start("https://www.ncbi.nlm.nih.gov/Structure/MMDB/docs/mmd
  b_search.html");
}

private void rCSBPDBToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.rcsb.org/pdb/home/home.do");
}

private void prositeToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://prosite.expasy.org/");
}

private void ensemblToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.ensembl.org/index.html");
}

private void uCSCGBToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://genome.ucsc.edu/cgi-bin/hgGateway");
}

private void entrezGenomesToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.ncbi.nlm.nih.gov/genome");
}

private void oMIMToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.ncbi.nlm.nih.gov/omim");
}

private void hapMapToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://hapmap.ncbi.nlm.nih.gov/");
}

private void hGMDToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.hgmd.org/");
}

private void geneticsHomeReferencesToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://ghr.nlm.nih.gov/");
}

private void dbSNPToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.ncbi.nlm.nih.gov/SNP/");
}

private void kEGGPathwaysDatabaseToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.genome.jp/kegg/pathway.html");
}

private void reactomeToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.reactome.org/");
}

private void pubmedToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.ncbi.nlm.nih.gov/pubmed");
}

private void pMCToolStripMenuItem_Click(object sender, EventArgs e)
```

```
        {
          System.Diagnostics.Process.Start("http://www.ncbi.nlm.nih.gov/pmc/");
        }

        private void bLASTToolStripMenuItem_Click(object sender, EventArgs e)
        {
          System.Diagnostics.Process.Start("http://blast.ncbi.nlm.nih.gov/Blast.cgi");
        }

        private void fASTAToolStripMenuItem_Click(object sender, EventArgs e)
        {
          System.Diagnostics.Process.Start("http://www.ebi.ac.uk/Tools/sss/fasta/");
        }

        private void clustalWToolStripMenuItem_Click(object sender, EventArgs e)
        {
          System.Diagnostics.Process.Start("http://www.genome.jp/tools/clustalw/");
        }

        private void mUSCLEToolStripMenuItem_Click(object sender, EventArgs e)
        {
          System.Diagnostics.Process.Start("https://www.ebi.ac.uk/Tools/msa/muscle/");
        }

        private void tcoffeeToolStripMenuItem_Click(object sender, EventArgs e)
        {
          System.Diagnostics.Process.Start("http://www.tcoffee.org/");
        }

        private void dALIToolStripMenuItem_Click(object sender, EventArgs e)
        {

          System.Diagnostics.Process.Start("http://ekhidna.biocenter.helsinki.fi/dali_lite/start
          ");
        }

        private void rCSBPDBProteinComparisonToolToolStripMenuItem_Click(object sender,
EventArgs e)
        {
          System.Diagnostics.Process.Start("http://source.rcsb.org/jfatcatserver/");
        }

        private void genScanToolStripMenuItem_Click(object sender, EventArgs e)
        {
          System.Diagnostics.Process.Start("http://genes.mit.edu/GENSCAN.html");
        }

        private void psiPredToolStripMenuItem_Click(object sender, EventArgs e)
        {
          System.Diagnostics.Process.Start("http://bioinf.cs.ucl.ac.uk/psipred/");
        }

        private void mfoldToolStripMenuItem_Click(object sender, EventArgs e)
        {
          System.Diagnostics.Process.Start("http://mfold.rna.albany.edu/?q=mfold/download-
mfold");
        }

        private void pHYLIPToolStripMenuItem_Click(object sender, EventArgs e)
        {

          System.Diagnostics.Process.Start("http://evolution.genetics.washington.edu/phylip.html
          ");
        }

        private void phyMLToolStripMenuItem_Click(object sender, EventArgs e)
        {
          System.Diagnostics.Process.Start("http://www.atgc-montpellier.fr/phyml/");
        }

        private void expasyToolsToolStripMenuItem_Click(object sender, EventArgs e)
        {
          System.Diagnostics.Process.Start("http://www.expasy.org/tools/");
        }

        private void sodiumToolStripMenuItem_Click(object sender, EventArgs e)
        {
          Form4 f4 = new Form4();
          f4.Show();
```

```
        }

        private void potassiumToolStripMenuItem_Click(object sender, EventArgs e)
        {
          Form5 f5 = new Form5();
          f5.Show();
        }

        private void calciumToolStripMenuItem_Click(object sender, EventArgs e)
        {
          Form6 f6 = new Form6();
          f6.Show();
        }

        private void chlorideToolStripMenuItem_Click(object sender, EventArgs e)
        {
          Form7 f7 = new Form7();
          f7.Show();
        }

        private void referenceSearchToolStripMenuItem1_Click(object sender, EventArgs e)
        {
          Form12 f12 = new Form12();
          f12.Show();
        }
    }
}
```

Result2.cs Code:

```
using System;
using System.Collections.Generic;
using System.ComponentModel;
using System.Data;
using System.Data.SqlClient;
using System.Diagnostics;
using System.Drawing;
using System.Linq;
using System.Text;
using System.Windows.Forms;

namespace Neurological_Channelopathic_Database
{
  public partial class Result2 : Form
  {
    string sql;
    SqlConnection con;
    DataSet ds;
    SqlDataAdapter sda;

    private string cname = string.Empty;
    private string gname = string.Empty;
    private string dname = string.Empty;
    private string slct1 = string.Empty;
    private string slct2 = string.Empty;

   public Result2(string _cname, string _gname, string _dname, string _slct1, string _slct2)
   {
     InitializeComponent();
     this.cname = _cname;
     this.gname = _gname;
     this.dname = _dname;
     this.slct1 = _slct1;
     this.slct2 = _slct2;
   }

   private void Result2_Load(object sender, EventArgs e)
   {
    try
    {
      string connectionString = "Data Source=.;Initial
Catalog=Neurological_Channelopathic_Database;User ID=sa;Password=1234";

      if (cname != "Enter Text Here")
      {
       if (gname != "Enter Text Here")
       {
```

```
        if (dname != "Enter Text Here")
        {
          if (slct1 == "AND")
          {
           if (slct2 == "AND")
           {
             sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' AND
Gene Like '%" + gname + "%' AND Disease_Caused Like '%" + dname + "%'";
           }
           else if (slct2 == " OR")
           {
             sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' AND
Gene Like '%" + gname + "%' OR Disease_Caused Like '%" + dname + "%'";
           }
           else if (slct2 == "NOT")
           {
             sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' AND
Gene Like '%" + gname + "%' AND NOT Disease_Caused Like '%" + dname + "%'";
           }
           else if (slct2 == "Select")
           {
             sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' AND
Gene Like '%" + gname + "%'";
           }
          }
          else if (slct1 == " OR")
          {
           if (slct2 == "AND")
           {
             sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' OR
Gene Like '%" + gname + "%' AND Disease_Caused Like '%" + dname + "%'";
           }
           else if (slct2 == " OR")
           {
             sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' OR
Gene Like '%" + gname + "%' OR Disease_Caused Like '%" + dname + "%'";
           }
           else if (slct2 == "NOT")
           {
             sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' OR
Gene Like '%" + gname + "%' AND NOT Disease_Caused Like '%" + dname + "%'";
           }
           else if (slct2 == "Select")
           {
             sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' OR
Gene Like '%" + gname + "%'";
           }
          }
          else if (slct1 == "NOT")
          {
           if (slct2 == "AND")
           {
             sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' AND
NOT Gene Like '%" + gname + "%' AND Disease_Caused Like '%" + dname + "%'";
           }
           else if (slct2 == " OR")
           {
             sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' AND
NOT Gene Like '%" + gname + "%' OR Disease_Caused Like '%" + dname + "%'";
           }
           else if (slct2 == "NOT")
           {
             sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' AND
NOT Gene Like '%" + gname + "%' AND NOT Disease_Caused Like '%" + dname + "%'";
           }
           else if (slct2 == "Select")
           {
             sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' AND
NOT Gene Like '%" + gname + "%'";
           }
          }
          else if (slct1 == "Select")
          {
           if (slct2 == "AND")
           {
             sql = "SELECT * FROM Channelopathy WHERE Gene Like '%" + gname + "%' AND
Disease_Caused Like '%" + dname + "%'";
           }
           else if (slct2 == " OR")
```

```
            {
              sql = "SELECT * FROM Channelopathy WHERE Gene Like '%" + gname + "%' OR
Disease_Caused Like '%" + dname + "%'";
            }
            else if (slct2 == "NOT")
            {
              sql = "SELECT * FROM Channelopathy WHERE Gene Like '%" + gname + "%' AND NOT
Disease_Caused Like '%" + dname + "%'";
            }
            else if (slct2 == "Select")
            {
              MessageBox.Show("Error! You have not selected a value from dropdown boxes: Please
search again");
              this.Close();
              Form3 f3 = new Form3();
              f3.Show();
            }
           }
          }
          else if (slct1 == "AND")
          {
            sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' AND
Gene Like '%" + gname + "%'";
          }
          else if (slct1 == " OR")
          {
            sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' OR
Gene Like '%" + gname + "%'";
          }
          else if (slct1 == "NOT")
          {
            sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%' AND
NOT Gene Like '%" + gname + "%'";
          }
          else if (slct1 == "Select")
          {
            MessageBox.Show("Error! You have not selected any option from dropdown box 1:
Please search again");
            this.Close();
            Form3 f3 = new Form3();
            f3.Show();
          }
         }
         else if (dname != "Enter Text Here")
         {
           MessageBox.Show("Please search with a valid search criteria by either using
individual text box search or using multiple text box search with dropdown box option");
           this.Close();
           Form3 f3 = new Form3();
           f3.Show();
         }
         else
         {
           sql = "SELECT * FROM Channelopathy WHERE Ion_Channels Like '%" + cname + "%'";
         }
        }
        else if (gname != "Enter Text Here")
        {
         if (dname != "Enter Text Here")
         {
          if (slct1 == "Select")
          {
           if (slct2 == "AND")
           {
             sql = "SELECT * FROM Channelopathy WHERE Gene Like '%" + gname + "%' AND
Disease_Caused Like '%" + dname + "%'";
           }
           else if (slct2 == " OR")
           {
             sql = "SELECT * FROM Channelopathy WHERE Gene Like '%" + gname + "%' OR
Disease_Caused Like '%" + dname + "%'";
           }
           else if (slct2 == "NOT")
           {
             sql = "SELECT * FROM Channelopathy WHERE Gene Like '%" + gname + "%' AND NOT
Disease_Caused Like '%" + dname + "%'";
           }
           else
           {
```

```
            MessageBox.Show("Error! You have not selected any option from dropdown box 2:
Please search again");
             this.Close();
             Form3 f3 = new Form3();
             f3.Show();
           }
          }
          else
          {
            MessageBox.Show("Please search with a valid search criteria by either using
individual text box search or using multiple text box search with dropdown box option");
            this.Close();
            Form3 f3 = new Form3();
            f3.Show();
          }
         }
         else
         {
           sql = "SELECT * FROM Channelopathy WHERE Gene Like '%" + gname + "%'";
         }
        }
        else if (dname != "Enter Text Here")
        {
          sql = "SELECT * FROM Channelopathy WHERE Disease_Caused Like '%" + dname + "%'";
        }
        else
        {
          MessageBox.Show("Please search with a valid search criteria by either using
individual text box search or using multiple text box search with dropdown box option");
          this.Close();
          Form3 f3 = new Form3();
          f3.Show();
        }

        con = new SqlConnection(connectionString);
        sda = new SqlDataAdapter(sql, con);
        ds = new DataSet();
        con.Open();
        sda.Fill(ds, "Channelopathy");
        con.Close();
        dataGridView1.DataSource = ds;
        dataGridView1.DataMember = "Channelopathy";
       }
       catch (Exception es)
       {
         Console.WriteLine(es.ToString());
       }
      }

      private void button1_Click(object sender, EventArgs e)
      {
        Form3 f3 = new Form3();
        f3.Show();
        this.Hide();
      }

      private void button2_Click(object sender, EventArgs e)
      {
        Form1 f1 = new Form1();
        f1.Show();
        this.Hide();
      }

      private void exportToExcelToolStripMenuItem_Click(object sender, EventArgs e)
      {
       if (dataGridView1.Rows.Count > 0)
       {
         Microsoft.Office.Interop.Excel.ApplicationClass XcelApp = new
Microsoft.Office.Interop.Excel.ApplicationClass();
         XcelApp.Application.Workbooks.Add(Type.Missing);

        for (int i = 1; i < dataGridView1.Columns.Count + 1; i++)
        {
          XcelApp.Cells[1, i] = dataGridView1.Columns[i - 1].HeaderText;
        }

        for (int i = 0; i < dataGridView1.Rows.Count; i++)
        {
         for (int j = 0; j < dataGridView1.Columns.Count; j++)
```

```
    {
      XcelApp.Cells[i + 2, j + 1] = dataGridView1.Rows[i].Cells[j].Value;
    }
   }
   XcelApp.Columns.AutoFit();
   XcelApp.Visible = true;
  }
 }

 private void closeToolStripMenuItem_Click(object sender, EventArgs e)
 {
   Application.Exit();
 }

 private void genBankToolStripMenuItem_Click(object sender, EventArgs e)
 {
   System.Diagnostics.Process.Start("https://www.ncbi.nlm.nih.gov/genbank//");
 }

 private void eMBLEBIToolStripMenuItem_Click(object sender, EventArgs e)
 {
   System.Diagnostics.Process.Start("http://www.ebi.ac.uk/");
 }

 private void uniProtKBToolStripMenuItem_Click(object sender, EventArgs e)
 {
   System.Diagnostics.Process.Start("http://www.uniprot.org/");
 }

 private void pIRToolStripMenuItem_Click(object sender, EventArgs e)
 {
   System.Diagnostics.Process.Start("http://pir.georgetown.edu/");
 }

 private void genpeptToolStripMenuItem_Click(object sender, EventArgs e)
 {
   System.Diagnostics.Process.Start("http://www.ncbi.nlm.nih.gov/protein");
 }

 private void sCOPToolStripMenuItem_Click(object sender, EventArgs e)
 {
   System.Diagnostics.Process.Start("http://scop.mrc-lmb.cam.ac.uk/scop/index.html");
 }

 private void cATHToolStripMenuItem_Click(object sender, EventArgs e)
 {
   System.Diagnostics.Process.Start("http://www.cathdb.info/");
 }

 private void fSSPToolStripMenuItem_Click(object sender, EventArgs e)
 {
   System.Diagnostics.Process.Start("http://protein.hbu.cn/fssp/");
 }

 private void mMDBToolStripMenuItem_Click(object sender, EventArgs e)
 {

  System.Diagnostics.Process.Start("https://www.ncbi.nlm.nih.gov/Structure/MMDB/docs/mmd
  b_search.html");
 }

 private void rCSBPDBToolStripMenuItem_Click(object sender, EventArgs e)
 {
   System.Diagnostics.Process.Start("http://www.rcsb.org/pdb/home/home.do");
 }

 private void prositeToolStripMenuItem_Click(object sender, EventArgs e)
 {
   System.Diagnostics.Process.Start("http://prosite.expasy.org/");
 }

 private void ensemblToolStripMenuItem_Click(object sender, EventArgs e)
 {
   System.Diagnostics.Process.Start("http://www.ensembl.org/index.html");
 }

 private void uCSCGBToolStripMenuItem_Click(object sender, EventArgs e)
 {
   System.Diagnostics.Process.Start("http://genome.ucsc.edu/cgi-bin/hgGateway");
```

```
}

private void entrezGenomesToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.ncbi.nlm.nih.gov/genome");
}

private void oMIMToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.ncbi.nlm.nih.gov/omim");
}

private void hapMapToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://hapmap.ncbi.nlm.nih.gov/");
}

private void hGMDToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.hgmd.org/");
}

private void geneticsHomeReferenceToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://ghr.nlm.nih.gov/");
}

private void dbSNPToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.ncbi.nlm.nih.gov/SNP/");
}

private void kEGGPathwaysDatabaseToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.genome.jp/kegg/pathway.html");
}

private void reactomeToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.reactome.org/");
}

private void pubmedToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.ncbi.nlm.nih.gov/pubmed");
}

private void pMCToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.ncbi.nlm.nih.gov/pmc/");
}

private void bLASTToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://blast.ncbi.nlm.nih.gov/Blast.cgi");
}

private void fASTAToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.ebi.ac.uk/Tools/sss/fasta/");
}

private void clustalWToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.genome.jp/tools/clustalw/");
}

private void mUSCLEToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("https://www.ebi.ac.uk/Tools/msa/muscle/");
}

private void tcoffeeToolStripMenuItem_Click(object sender, EventArgs e)
{
  System.Diagnostics.Process.Start("http://www.tcoffee.org/");
}

private void dALIToolStripMenuItem_Click(object sender, EventArgs e)
{
```

```
        System.Diagnostics.Process.Start("http://ekhidna.biocenter.helsinki.fi/dali_lite/start
        ");
      }

      private void rCSBPDBProteinComparisonToolToolStripMenuItem_Click(object sender,
EventArgs e)
      {
        System.Diagnostics.Process.Start("http://source.rcsb.org/jfatcatserver/");
      }

      private void genScanToolStripMenuItem_Click(object sender, EventArgs e)
      {
        System.Diagnostics.Process.Start("http://genes.mit.edu/GENSCAN.html");
      }

      private void psiPredToolStripMenuItem_Click(object sender, EventArgs e)
      {
        System.Diagnostics.Process.Start("http://bioinf.cs.ucl.ac.uk/psipred/");
      }

      private void mfoldToolStripMenuItem_Click(object sender, EventArgs e)
      {
        System.Diagnostics.Process.Start("http://mfold.rna.albany.edu/?q=mfold/download-
mfold");
      }

      private void pHYLIPToolStripMenuItem_Click(object sender, EventArgs e)
      {

        System.Diagnostics.Process.Start("http://evolution.genetics.washington.edu/phylip.html
        ");
      }

      private void phyMLToolStripMenuItem_Click(object sender, EventArgs e)
      {
        System.Diagnostics.Process.Start("http://www.atgc-montpellier.fr/phyml/");
      }

      private void expasyToolsToolStripMenuItem_Click(object sender, EventArgs e)
      {
        System.Diagnostics.Process.Start("http://www.expasy.org/tools/");
      }

      private void sodiumToolStripMenuItem_Click(object sender, EventArgs e)
      {
        Form8 f8 = new Form8();
        f8.Show();
      }

      private void potassiumToolStripMenuItem_Click(object sender, EventArgs e)
      {
        Form9 f9 = new Form9();
        f9.Show();
      }

      private void calciumToolStripMenuItem_Click(object sender, EventArgs e)
      {
        Form10 f10 = new Form10();
        f10.Show();
      }

      private void chlorideToolStripMenuItem_Click(object sender, EventArgs e)
      {
        Form11 f11 = new Form11();
        f11.Show();
      }

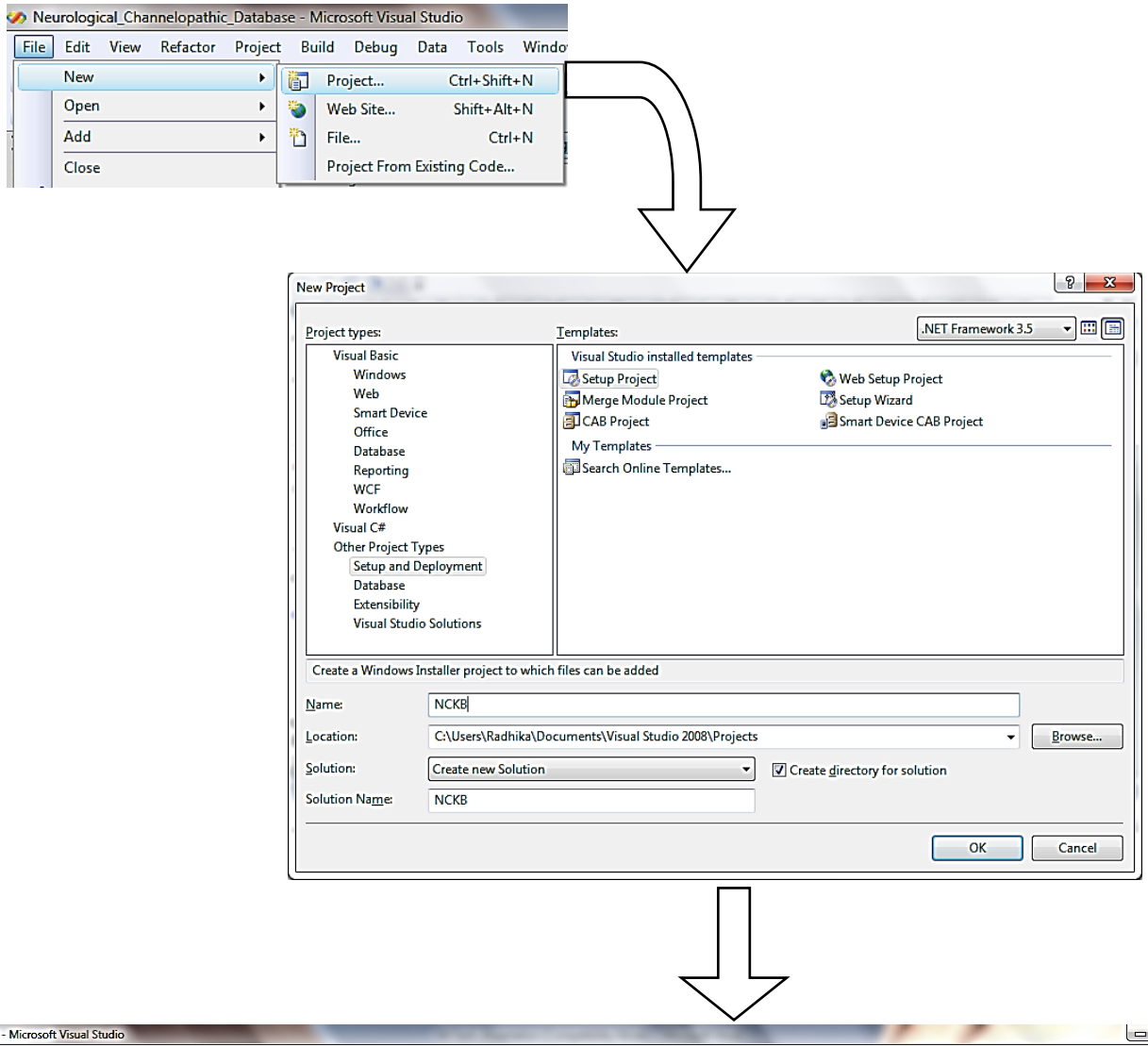
      private void referenceSearchToolStripMenuItem1_Click(object sender, EventArgs e)
      {
        Form12 f12 = new Form12();
        f12.Show();
      }
   }
}
```

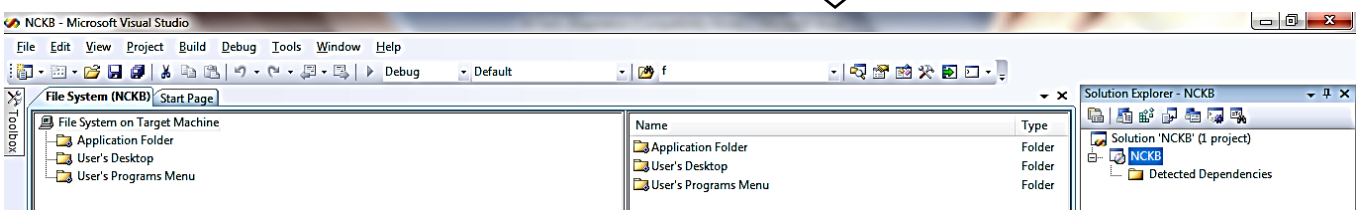
4.2.4 Packaging of Software:

a. Build a 'Setup' for the project.
b. Write a 'Script file' that can be used for creating database into another system.

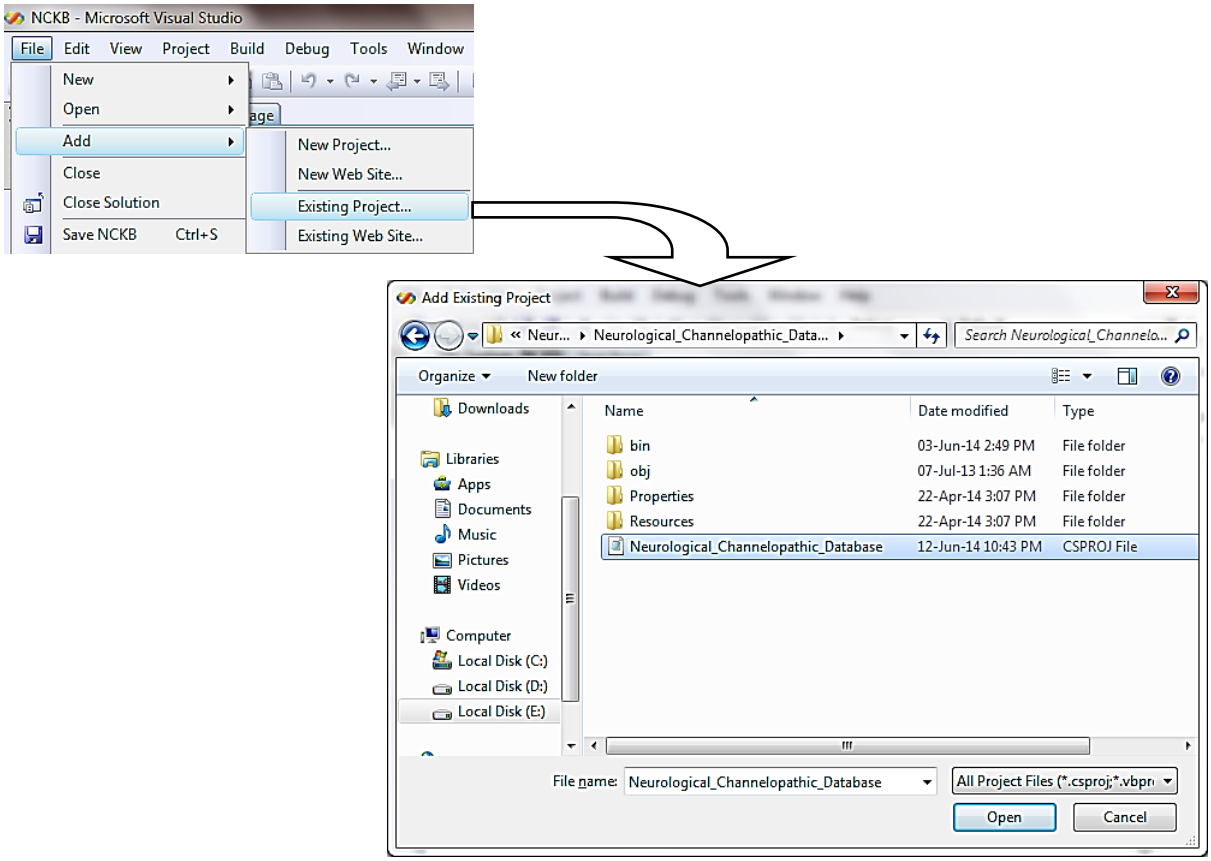
a. Steps for building a 'Setup' for the Project:

i. Create new setup project.

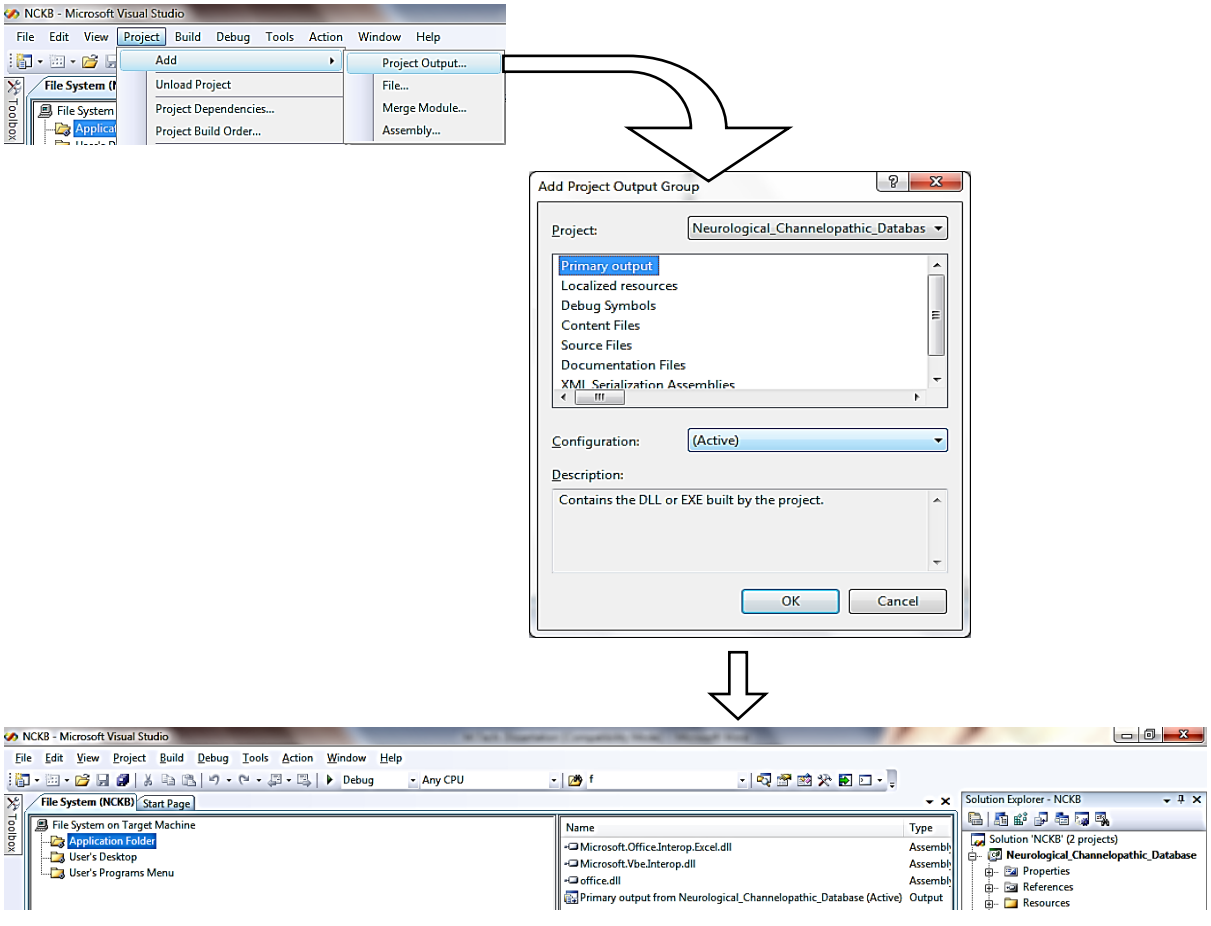




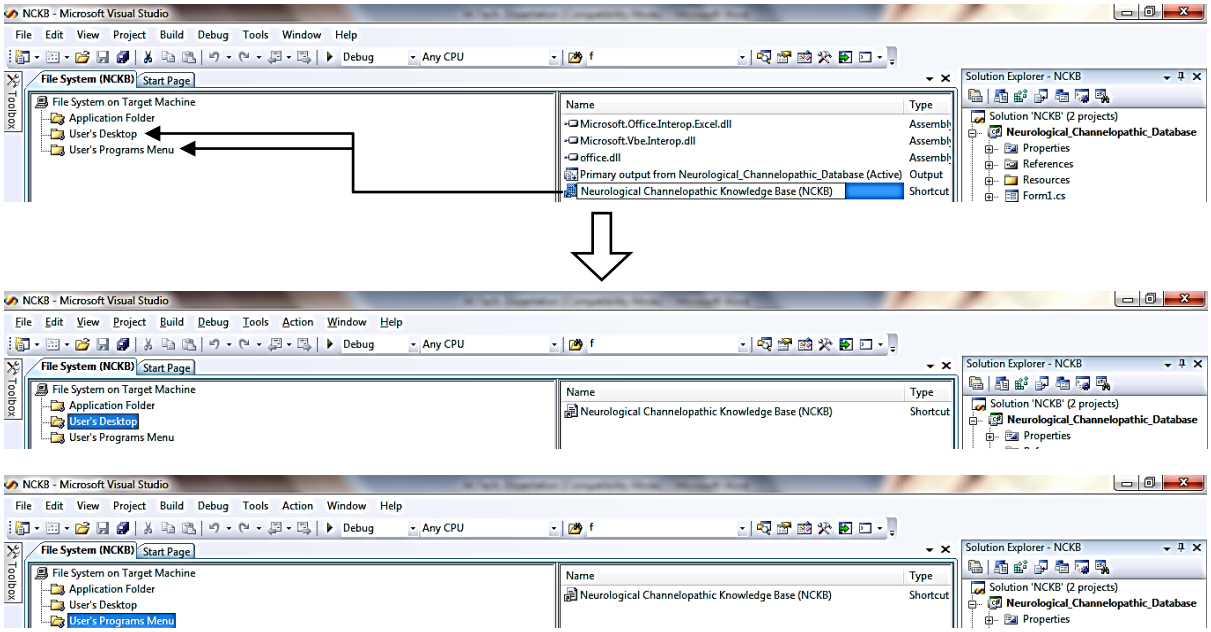
ii. Add existing project.



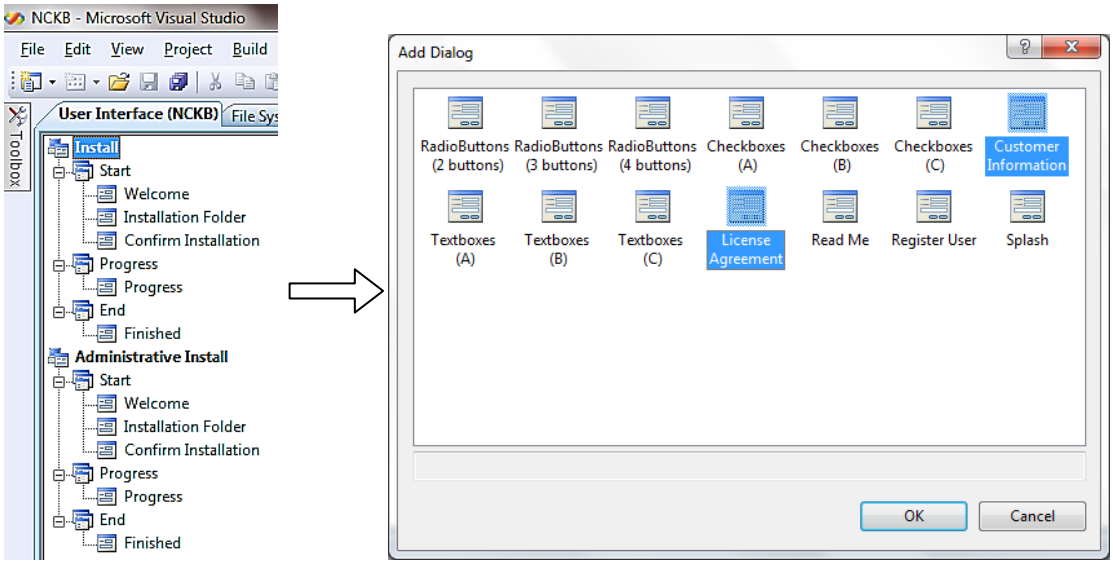
iii. Add Project output.



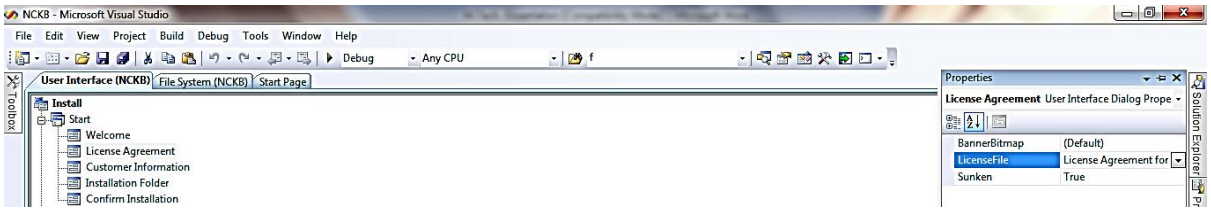
iv. Create shortcut for ‘Primary output from Neurological_Channelopathic_Database (Active)’ and Copy it into both ‘User’s Desktop’ folder and ‘User’s Programs Menu’ folder.



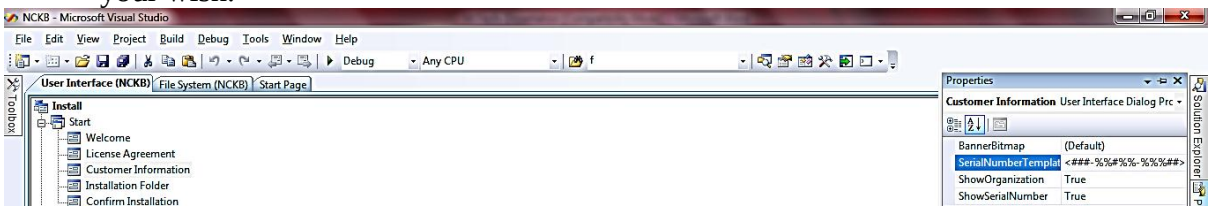
v. Add Dialogs: Click on ‘User Interface Editor’ then Right click on ‘Start’ and choose ‘Add Dialog’



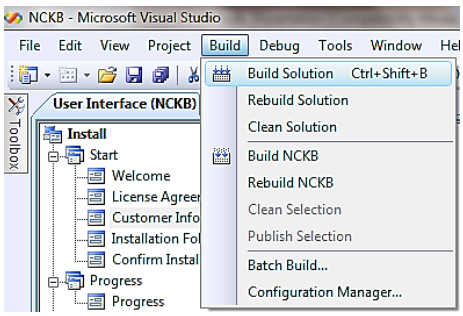
vi. Add License agreement file: Right click on ‘License Agreement’ and choose ‘Properties Window’ and add License agreement file from the computer.



vii. Set product key: Right click on 'Customer Information' and then change 'ShowSerialNumber' to 'True'. Modify the Serial Number Template according to your wish.



viii. Build Solution



Project has been build successful.

b. Script File:

```
go
create database Neurological_Channelopathic_Database;
go
use Neurological_Channelopathic_Database;
create table Channelopathy (Tissue_affected nvarchar(MAX), Ion_channels nvarchar(MAX), Gene nvarchar(MAX), Channel_subunit nvarchar(MAX), Disease_caused nvarchar(MAX), Symptoms nvarchar(MAX), Mechanism nvarchar(MAX), Reference nvarchar(MAX));
insert into Channelopathy values ('Skeletal muscle','Cl Channel','ClCN1','ClC-1 (Chloride channel protein 1)','Myotonia congenita','Muscle stiffness, inability to relax after contraction','Mutated channel either become nonfunctional or open at a more depolarized potential thus losses chloride conductance thereby increasing the time taken for repolarization due to which muscle hyperexcitability takes place thus causing myotonia','(Lee et al., 2013) (Duran et al., 2010) (Lossin and George., 2008) (Koch et al., 1992)');
insert into Channelopathy values ('Skeletal muscle','Cl Channel','ClCN1','ClC-1 (Chloride channel protein 1)','Thomsen s disease','Proximal muscle weakness, myalgia and muscular hypertrophy','Mutated channels results in moderate decrease in chloride conduction and following the above mentioned molecular mechanism it causes mild symptoms','(Wu et al., 2002) (Kubisch et al., 1998) (Koch et al. 1992)');
insert into Channelopathy values ('Skeletal muscle','Cl Channel','ClCN1','ClC-1 (Chloride channel protein 1)','Becker's disease','Muscle hypertrophy and distal muscle weakness','Mutated channel proteins have not get expressed to the optimum level thereby causing great reduction in choride conduction and thus causing myotonia by following the above mentioned mechanism','(Graves and Hanna., 2005) (Wu et al., 2002) (Kubisch et al., 1998)');
insert into Channelopathy values ('Skeletal muscle','Nav Channel','SCN4A','Nav1.4 (Sodium channel protein type 4 subunit alpha)','Potassium-aggravated myotonia (PAM)','Sustained muscle tension and inability to relax muscle','The altered channels upregulate the sodium ion influx into the skeletal muscles thereby triggering prolonged muscle contractions due to one or more of the following reasons for instance reduced fast channel inactivation, enhanced recovery rate from fast inactivation, slowed deactivation or hyperpolarizing shift in steady state activation','(Orrell et al., 1998) (Cummins and Bendahhou., 2009) (Vicart et al., 2005)');
insert into Channelopathy values ('Skeletal muscle','Nav Channel','SCN4A','Nav1.4 (Sodium channel protein type 4 subunit alpha)','Para-myotonia congenita (PMC)','Cold sensitive myotonia and episodic muscular weakness','Mutated sodium channels exhibit slowed inactivation and faster recovery from inactivation thus causing hyperexcitability of muscles (myotonia) and sometimes inexcitability that causes episodic weakness in muscles','(Heine et al., 1993) (McClatchey et al.,1992) (Ptacek et al., 1992) (Tamaoaka, A. 2003) (Vicart et al., 2005)');
insert into Channelopathy values ('Skeletal muscle','Nav Channel','SCN4A','Nav1.4 (Sodium channel protein type 4 subunit alpha)','Hyper-kalemic periodic paralysis (hyperKPP)','Extreme muscle weakness and increased level of potassium during attacks','Due to altered anchoring site of fast inactivation particle in mutated channel, persistent sodium current takes place that causes depolarization of the cell thereby inactivating other normal sodium channels due to the absence of action potential','(Bendahhou et al., 2002) (Ptacek et al., 1991) (Rojas et al., 1991)');
insert into Channelopathy values ('Skeletal muscle','Nav & Cav Channel','SCN4A and CACNA1S','NaV1.4 (Sodium channel protein type 4 subunit alpha) CaV1.1 (Voltage-dependent L-
```

```
type calcium channel subunit alpha-1S)','Hypo-kalemic periodic paralysis (hypoKPP)','Extreme muscle weakness associated with low potassium level in serum','Mutated sodium and calcium channels are responsible for abnormal gating pore currents i.e. shift in the resting membrane potential to a more depolarized second stable state (paradoxical depolarization). Moreover due to their affected voltage sensing capability deregulated flow of Ca2+ and Na+ ions into the muscles take place thereby causing reduced contractibility of muscles and ultimately muscle weakness','(Sokolov et al., 2010) (Jurkat-Rott et al., 2009) (Sokolov et al., 2007) (Bulman et al., 1999) (Jurkat- Rott et al., 1994) (Ptacek et al., 1994)');
insert into Channelopathy values ('Peri-pheral Nerve','Nav Channel','SCN9A','Nav1.7 (Sodium channel protein type 9 subunit alpha)','Primary erythro-melalgia','Burning pain, flushing and swelling of the feet, hands and sometimes other areas','Mutated sodium channels exhibit hyperpolarizing shift toward activation and slowed inactivation kinetics that makes opening of channel more easiar and prolonged. Thus increased inflow of sodium ions enhances transmission of pain signals, leading to the signs and symptoms of erythromelalgia','(Dib-Hajj et al., 2005) (Waxman et al., 2005a & b) (Estacion et al., 2011)');
insert into Channelopathy values ('Peri-pheral Nerve','Nav Channel','SCN9A','Nav1.7 (Sodium channel protein type 9 subunit alpha)','Paroxysmal extreme pain disorder (PEPD)','Burning pain and flushing in the sub-mandibular, ocular, and rectal areas','Mutated sodium channels that expressed in nociceptive dorsal root ganglion and sympathetic ganglion neurons cannot be able to close as quickly as usual leading to prolonged transmission of pain signals. Moreover we can say that gain of function mutations result in increased action potential duration and therefore more synaptic transmission thus causing heightened pain perception','(Fertleman et al., 2007) (Lampert et al., 2010)');
insert into Channelopathy values ('Peri-pheral Nerve','Nav Channel','SCN9A','Nav1.7 (Sodium channel protein type 9 subunit alpha)','Congenital in-sensitivity to pain (CIP)','Complete loss of pain sensation','Mutated channel exhibit complete functional loss that leads to an inability to form action potentials and therefore loss of pain sensation','(Cox et al., 2006) (Goldberg et al., 2007)');
insert into Channelopathy values ('Central Nervous System','Kv, Cav, Channel and Glutamate transporter','KCNA1 CACNA1A CACNB4 SLC1A3','Kv1.1 (Potassium channel sub-family A member 1) Cav2.1 (Calcium channel Subunit alpha), Sodium-dependent glutamate/ aspartate transporter1','Episodic ataxias','Problems with movements, poor coordination and balance','These genes alter the transport of ions and glutamate into the brain that causes certain neurons to become overexcited and disrupts normal communication between these cells. Moreover it also results in decreased current often due to protein instability. Furthermore potassium channels are vital in down stroke of action potential and its mutation cause prolonged action potential and altered excitability of different neuronal population','(Jen et al., 2007) (Wan et al., 2005) (Browne et al., 1994) (Zerr et al., 1998)');
insert into Channelopathy values ('Central Nervous System','Kv Channel','KCNMA1','Kca (Potassium large conductance calcium-activated channel, subfamily M, alpha member 1)','Paroxysmal dyskinesias','Sudden, unpredictable disabling attacks of involuntary movements','Mutated channels formed due to altered KCNMA1 gene promotes excitability of neurons by inducing rapid repolarization of action potential that allows neurons to conduct at a faster rate thereby causing recurrent attacks','(Lee and Cui., 2009) (Du et al., 2005)');
insert into Channelopathy values ('Central Nervous System','Kv Channel','KCNQ2 KCNQ3','Kv7.2 & Kv7.3 (Potassium voltage-gated channel subfamily KQT member 2 & 3)','Benign familial neonatal seizures (BFNS)','Recurrent seizures in newborn babies, muscle rigidity, convulsions, and loss of consciousness','Channels coded by KCNQ2 and KCNQ3 genes transmit M-currents that ensure normal shutting of active neuron, while mutated genes result in reduced or altered M-current which cause excessive excitability of neurons that results in the development of seizures in brain','(Biervert et al.,1998) (Singh et al., 1998) (Charlier et al., 1998) (Castaldo et al., 2002)');
insert into Channelopathy values ('Central Nervous System','Nav Channel','SCN1A SCN1B','NaV1.1 (Sodium channel type 1 subunit alpha)','Generalized epilepsy with febrile seizures (GEFS)','It is characterized by a long term recurring seizures','However, it arises from many causes that include metabolic brain disorders, abnormalities of cortical development, brain trauma or structural lesions of the brain (brain tumors), while mutated channel is also one of the prominent factor that causes overexcitation of neurons and ultimately epilepsy with seizures','(Catterall et al., 2010) (Tan et al., 2012) (Xu et al., 2012)');
insert into Channelopathy values ('Central Nervous System','Cav & Nav Channels','CACNA1A ATP1A2 SCN1A','Cav2.1 (Calcium channel Subunit alpha) ATP1A2 (ATPase subunit alpha-2) NaV1.1 (Sodium channel type 1 subunit alpha)','Familial hemiplegic migraine (FHM)','Intense, throbbing pain in one area of the head, often accompanied by nausea, vomiting, and extreme sensitivity to light and sound','Altered channels formed by these mutated genes disrupt the normal release and re uptake of certain neurotransmitters in brain that result in the alteration of signaling between neurons thereby causing hemiplegic migraine. Moreover these mutated genes cause three different types of Familial hemiplegic migraine that are CACNA1A mutations cause FHM1, ATP1A2 mutations cause FHM2 and SCN1A mutations cause FHM3','(Pietrobon, D. 2010) (Cestele et al., 2008) (Gritz et al., 2013) (Pelzer et al., 2013) (Ducros et al., 2001)');
insert into Channelopathy values ('Central Nervous System','Cav Channel','CACNA1A','Cav2.1 (Calcium channel Subunit alpha)','Spino-cerebellar ataxia type-6 (SCA6)','Progressive pure cerebellar ataxia, poor coordination of hands, speech, and eye movements, Impaired speech, Patient progressively lose physical control','Expansion of CAG repeats were found at the 3’ region that generates poly glutamine tract thereby producing abnormally extended α1 subunit of calcium channel that abnormally aggregate calcium channel protein thereby affecting neurotransmitter’s release in the brain eventually causing death of neurons','(Graves and Hanna., 2005) (Denier et al., 1999) (Rajakulendran et al., 2010) (Zhuchenko., et al., 1997)');
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insert into Channelopathy values ('Heart','Kv and Nav Channels','KCNE1 KCNE2 KCNH2 KCNQ1 KCNJ2 SCN5A','Kv (Voltage gated potassium channel subfamily E member 1 &2, subfamily H member 2, subfamily Q member 1, subfamily J member 2), Nav (Sodium channel protein type 5 subunit alpha)','Cardiac arrhythmia','Dizziness, palpitations, syncope, deficits in executive function and abstract reasoning, even cause death','Irregularities in heart rythm viz mutated channel is reported due to triggered activity, which involves impulse initiation due to the membrane potential oscillations occurring just after an action potential that results in abnormal transmission of electrical impulse in the heart cell thereby causing aberrant cardiac rhythm','(Schimpf et al., 2013) (Campuzano et al., 2010)');
insert into Channelopathy values ('Heart','Inward Rectifier Potassium (Kir) Channel','KCNJ2','Kir2.1 (Inwardly rectifying potassium channel subfamily J member 2)','Andersen-Tawil syndrome (ATS)','Muscle weakness (periodic paralysis), changes in heart rhythm(arrhythmia) and developmental abnormalities like widespread eyes, cleft palate and syndactyly of the toes','Mutations in the KCNJ2 gene alter the usual structure and function of potassium channels that prevent the channels from being inserted correctly into the cell membrane. Moreover it also prevent binding of PIP2 that disrupt the flow of potassium ions in skeletal and cardiac muscles thus leading to periodic paralysis and irregular heart rhythm','(Plaster et al., 2001) (Tristani-Firouzi et al., 2010) (Donaldson et al., 2004) (Tristani-Firouzi et al., 2002)');
insert into Channelopathy values ('Heart','Inward Rectifier Potassium (Kir) Channel','KCNJ10','Kir4.1 (ATP-dependent inwardly rectifying potassium channel Kir4.1)','SeSAME syndrome and EAST syndrome','Characterized by generalized seizures with onset in infancy, delayed psychomotor development, ataxia, sensorineural hearing loss, hypokalemia, metabolic alkalosis and hypomagnesemia','Mutated inward rectifier potassium channel disrupts the potassium buffering action of glial cells in the brain and disturbs the homeostasis of potassium ions in various organs like inner ear, retina and kidney thus exhibiting the symptoms of SeSAME','(Bockenhauer et al., 2009) (Scholl et al.,2009)');
insert into Channelopathy values ('Heart','Kv Channel','KCNE1 & KCNQ1','Kv (Potassium voltage gated channel subfamily E member 1,subfamily Q member1)','Jervell and Lange-Nielson syndrome (J-LN)','Cardiac arrhythmia concomitant with deafness','Mutated genes affect potassium channel structure and function thereby preventing the assembly of normal channels. These changes disrupt the flow of potassium ions in the inner ear and in cardiac muscle, leading to hearing loss and an irregular heart rhythm','(Schulze-Bahr et al., 1997) (Schwartz et al., 2006) (Wang et al., 2002)');
create table Channelopedia (Channel_name nvarchar(MAX), Subtypes nvarchar(MAX), Gene nvarchar(MAX), Tissue_specificity nvarchar(MAX), Subcellular_location nvarchar(MAX), Subunit_structure nvarchar(MAX), Physiological_role nvarchar(MAX), Involvement_in_disease nvarchar(MAX), Reference nvarchar(MAX));
insert into Channelopedia values ('Sodium (NaV) Channel','NaV 1.1','SCN1A','Adult brain, especially in Purkinje cells','Cell bodies','Nav type-1 α-subunit Homotetradomain. Each domain consists of internally repeated segments (S1-S6)','Control of action potential generation and propagation','Myoclonic epilepsy','(Kalume et al., 2007) (Spampanato et al., 2003)');
insert into Channelopedia values ('Sodium (NaV) Channel','NaV 1.2','SCN2A','Central neurons, peripheral neurons','Axon initial segment of Cerebellar granule cells','Nav type-2 α-subunit Homotetradomain. Each domain consists of internally repeated segments (S1-S6)','Control of action potential generation and propagation','Inherited febrile seizures','(Kearney et al., 2001) (Shi et al., 2012)');
insert into Channelopedia values ('Sodium (NaV) Channel','NaV 1.3','SCN3A','Developing CNS, peripheral neurons and cardiac myocytes','Membrane','Nav type-3 α-subunit Homotetradomain. Each domain consists of internally repeated segments (S1-S6)','Fast activation and Inactivation Kinetics','Hyperexcitability in epileptic patient','(Estacion et al.,2010)');
insert into Channelopedia values ('Sodium (NaV) Channel','NaV 1.4','SCN4A','Skeletal muscle','Membrane','Nav type-4 α-subunit Homotetradomain. Each domain consists of internally repeated segments (S1-S6)','Generation and propagation of action potentials that initiate muscle contraction','Several myotonia and periodic paralysis disorders, Arrhythmias','(Anyukhovsky et al., 2011)');
insert into Channelopedia values ('Sodium (NaV) Channel','NaV 1.5','SCN5A','Brain, cardiac muscle','Axon, Co-localized with Neurofilaments','Nav type-5 α-subunit Homotetradomain. Each domain consists of internally repeated segments (S1-S6','Action potential generation & propagation in cardiac tissue and brain','Syncope, Seizures, Cardiac arrhythmias Long QT syndrome (LQTS), Brugada syndrome, Cardiac conduction disease','(Hu et al., 2010) (Tan et al., 2007)');
insert into Channelopedia values ('Sodium (NaV) Channel','NaV 1.6','SCN8A','Cerebellar granule cells','Mature nodes along compact myelinated axons, dendrites','Nav type-8 α-subunit Homotetradomain. Each domain consists of internally repeated segments (S1-S6)','Most prominently expressed and potential generation in various types of tissues','Cognitive impairment with or without cerebellar ataxia (CIAT), Epileptic encephalopathy, early infantile, type 13 (EIEE13)','(Trudeau et al., 2006) (Osorio et al., 2005)');
insert into Channelopedia values ('Sodium (NaV) Channel','Nav 1.7','SCN9A','Nociceptors (Nerves transmitting pain signals)','Membrane','Nav type-9 α-subunit Homotetradomain. Each domain consists of internally repeated segments (S1-S6)','Responsible for carrying pain signals to brain','Erythromelalgia, Paroxysmal extreme pain disorder, Congenital insensitivity to pain(CIP)','(Cregg et al., 2013) (Estacion et al., 2011) (Klein et al., 2013)');
insert into Channelopedia values ('Sodium (NaV) Channel','Nav 1.8','SCN10A','Peripheral sensory nervous system','Membrane','Nav type-10 α-subunit Homotetradomain. Each domain consists of internally repeated segments (S1-S6)','Transmits pain signals to CNS in cold temperature','Pain and Paresthesias','(Faber et al., 2012)');
insert into Channelopedia values ('Sodium (NaV) Channel','Nav 1.9','SCN11A','Heart and Dorsal root ganglion neurons','Trigeminal neurones and their axons','Nav type-11 α-subunit
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Homotetradomain. Each domain consists of internally repeated segments (S1-S6)','Involved in pain related signalling','Mechanical and Heat pain hypersensitivity','(Lolignier et al., 2011)');
insert into Channelopedia values ('Sodium (NaV) Channel','NaV β1','SCN1B','Muscle and Neuronal cells','Membrane','Nav type-1 β-subunit. Single domain. Auxiliary subunit','Modulate channel gating kinetics','Brugada syndrome, Generalized epilepsy with febrile seizures plus type 1','(Audenaert et al., 2003) (Patino et al., 2011)');
insert into Channelopedia values ('Sodium (NaV) Channel','NaV β2','SCN2B','White matter tracts in the cerebellum,Hippocampal, cortical pyramidal neurons, and cerebellar purkinje neurons','At the membrane of  Cell bodies and Nodes of Ranvier','Nav type-2 β-subunit. Single domain. Auxiliary subunit','Modulate channel gating kinetics','Brugada syndrome','(Riuro et al., 2013)');
insert into Channelopedia values ('Sodium (NaV) Channel','NaV β3','SCN3B','Contractile myocardium','Membrane','Nav type-3 β-subunit. Single domain. Auxiliary subunit','Modulate channel gating kinetics','Brugada syndrome type 7','(Hu et al., 2009) (Carmen et al., 2010)');
insert into Channelopedia values ('Sodium (NaV) Channel','NaV β3','SCN3B','Dorsal root ganglia','Membrane','Nav type-4 β-subunit. Single domain. Auxiliary subunit','Modulate channel gating kinetics','Long QT-syndrome type 10','(Medeiros-Domingo et al., 2007)');
insert into Channelopedia values ('Potassium (Kv) Channel','Kv1.1','KCNA1','Unmyelinated Axons, Cell Somas, Axon Terminals, Dendrites','Membrane, Transmembrane','Kv shaker member 1, α-subunit consist of six helical segments (S1-S6)','Circadian Rhythms, Neuronal Firing','Episodic Ataxia Type 1, Myokymia, Periodic Ataxia','(Orazio et al., 2012) (Brew et al., 2003) (Shook et al., 2008)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv1.2','KCNA2','Hippocampal Neuron Neocortex, Main olfactory bulb (MOB) and Cerebellum','Membrane, Multi-pass membrane protein','Kv shaker member 2, α-subunit consist of six helical segments (S1-S6)','Regulation of state Transitions and Repetitive activity in Striatal Medium Spiny Neurons','Cerebellar Ataxia, myokymia and neuromyotonia','(Pruss et al., 2009) (Lorincz and Nusser., 2008)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv1.3','KCNA3','Effector memory T-cells','Membrane, Multi-pass membrane protein','Kv shaker member 3, α-subunit consist of six helical segments (S1-S6)','Regulate several physiological functions of Lymphocytes, Cell Proliferation','Down syndrome Neural Progenitors','(Wulff et al., 2003) (Cidad et al., 2012)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv1.4',' KCNA4','Heart, Cerebellum','Membrane, Multi-pass membrane protein','Kv shaker member 4, α-subunit consist of six helical segments (S1-S6)','Modulating Electrophysiological Behaviour','Chronic Pancreatitis, Hyperalgesia ','(Chandy et al., 2004) (Freedman et al., 1992) (Leonard et al., 1992)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv1.5','KCNA5','Heart, Brain','Cell membrane, Multi-pass membrane protein','Kv shaker member 5, α-subunit consist of six helical segments (S1-S6)','Physiological processes in Brain and Muscle','Ischemia Affects','(Fedida et al., 2003) (Gobrit et al., 2007) (Vicente et al., 2006) (Archer et al., 2001) (Stapels et al., 2010)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv1.6','KCNA6','Ganglion Cell','Membrane, Multi-pass membrane protein','Kv shaker member 6, α-subunit consist of six helical segments (S1-S6)','Mediates the voltage-dependent potassium ion permeability of excitable membranes','Myokymia and Neuromyotonia','(van Poucke et al., 2012)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv1.7','KCNA7','Heart,Kidney, Skeletal Muscle','Membrane, Multi-pass membrane protein','Kv shaker member 7, α-subunit consist of six helical segments (S1-S6)','Important  Role in the Repolarization of Cell Membranes','Acute myeloid leukemiacute Myeloid Leukemia','(Finol-Urdaneta et al., 2006) (Kashuba et al., 2001)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv2.1','KCNB1','CNS','Pyramidal Neurons in Cortex','Kv shab member 1, α-subunit consist of six helical segments (S1-S6)','Regulates Neuronal Excitability, Action Potential Duration and Tonic Spiking','Hyperalgesia','(Misonou et al., 2005)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv2.2','KCNB2','Trapezoid body neurons','Trapezoid body neurons','Kv shab member 2, α-subunit consist of six helical segments (S1-S6)','Regulate Action Potential Firing','Cardiovascular disease risk','(Johnston et al., 2008) (Kihira et al., 2010)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv3.1','KCNC1','Cortex, Cerebellum, Hippocampus Neurons in the Globus Pallidus, CNS','Hippocampus Neurons in the Globus Pallidus','Kv shaw member 1, α-subunit consist of six helical segments (S1-S6)','Involved in Motor Control','Ataxia with prominent Hypermetria, Constitutive Hyperactivity, Sleep Loss, Impaired Motor performance, Tremor and Myoclonus','(Lewis et al., 2004) (Espinosa et al., 2008)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv3.2','KCNC2','Cortical GABAergic Interneurons, Hippocampus Somatic, Proximal Dendritic Membrane Axons','Proximal Dendritic Membrane Axons, Cortical GABAergic Interneurons','Kv shaw member 2, Homo- or heterotetramer, α-subunit consist of six helical segments (S1-S6) ','Neurodevelopmental delay Cerebellar Ataxia','Susceptibility to Seizures','(Chow et al., 1999) (Lau et.al., 2000)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv3.3','KCNC3','Cortex, Basal Ganglia and Cerebellum','Membrane, Multi-pass membrane protein','Kv shaw member 3, Homo- or heterotetramer, α-subunit consist of six helical segments (S1-S6)','Involved in Motor Control','Constitutive Hyperactivity, Sleep Loss, Impaired Motor Performance, Ataxia, Tremor and Myoclonus','(Espinosa et al., 2008)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv4.1','KCND1','Epithelial Cells, Alveolar and Mammary Epithelial Cells, Adipose Tissue-Derived Stem Cells','Multi-pass membrane protein,  Alveolar  Mammary Epithelial Cells  Adipose Tissue-Derived Stem Cells','Kv shal
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member 1, Homotetramer, α-subunit consist of six helical segments (S1-S6)','Contribute to cell Migration and Wound Healing','Gastric Cancer NOS, Malignant Neoplasm of Breast','(Sandhiya and Dkhar., 2009)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv4.2','KCND2','Brain','Localized in the Dendrites near Postsynaptic Regions','Kv shal member 2, Homotetramer, α-subunit consist of six helical segments (S1-S6)','Regulate Synaptic Plasticity','Cardiovascular disease','(Jo et al., 2010)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv4.3','KCND3','Rat Adult Brain and Heart Tissues','Molecular layer Interneurons','Kv shal member 3, Homotetramer, α-subunit consist of six helical segments (S1-S6)','Internalized in response to Glutamatergic stimulation in Purkinje Cells, Neuronal Somatodendritic Interactions','Spinocerebellar Ataxia Type 1, Cerebellar Ataxia','(Hourez et al., 2011)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv7.2','KCNQ2','Peripheral Nerve System','Membrane, Multi-pass membrane protein','Kv KQT like Subfamily member 2, Heteromultimer, α-subunit consist of six helical segments (S1-S6)','Regulate Neurotransmitter Release, Heart Rate, Insulin Secretion, Neuronal Excitability, Epithelial electrolyte Transport, Smooth Muscle contraction','Myokymia and Neuromyotonia','(van Poucke et al., 2012)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv7.3','KCNQ3','Distributed Broadly in Brain','Membrane, Multi-pass membrane protein','Kv KQT like Subfamily member 3, Heteromultimer, α-subunit consist of six helical segments (S1-S6)','Electrical Hyperexcitability in BFNC','Familial Neonatal Convulsions (BFNC), Autosomal Dominant Epilepsy of Infancy, Myokymia','(Schroeder et al., 1998) (Chung et al., 2006)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv7.4','KCNQ4','Almost All Brain Regions','Discrete Nuclei Of Brainstem, Including the Mid- Brain ','Kv KQT like Subfamily member 4, Homo/Heterotetramer, α-subunit consist of six helical segments (S1-S6)','Participate in both pre- and Postsynaptic Modulation of basal and stimulated excitatory Neurotransmission','Chinese Non-Syndromic Hearing Loss Pedigree','(Kharkovets et al., 2000)');
insert into Channelopedia values ('Potassium (Kv) Channel','kv7.5','KCNQ5','Neocortex and the Hippocampal','Apical and Lateral Membranes','Kv KQT like Subfamily member 5, Heteromultimer , α-subunit consist of six helical segments (S1-S6)','Controlling Basal Anion Secretion','Epilepsy','(Yus-Najera et al., 2003)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav1.1','CACNA1S','Skeletal Muscle','Cell Junction , Postsynaptic Cell Membrane','Cav L-type, α-1S subunit, Each α1 subunit consists of 6 helical transmembrane segments (S1-S6)','Functions as a Voltage Sensor in Skeletal Muscle Excitation-Contraction Coupling','Hypokalemic Periodic Paralysis, Thyrotoxic Periodic paralysis and Malignant Hyperthermia Susceptibility','(Kung et al., 2004) (Kim et al., 2001)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav1.2','CACNA1C','Brain, Heart, Ovary Neurons','Membrane; Multi-pass membrane protein','Cav L-type, α-1C subunit, Each α1 subunit consists of 6 helical transmembrane segments (S1-S6)','Release of Hormones and Neurotransmitters','Vision, Hearing, and Gene Expression','(Kameda et al., 2006) (Reuter H. 1983)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav1.3','CACNA1D','Auditory Brainstem, CenterAuditory Sensory hair Cells, Neuronal Cells and Some Epithelial Cells','Somatodendritic Compartment of many Types of Neurones','Cav L-type, α-1D subunit, Each α1 subunit consists of 6 helical transmembrane segments (S1-S6)','Regulate Intracellular Processes such as Contraction, Secretion, Neurotransmission and Gene Expression','Deafness','(Roberts et al., 1990) (Satheesh et al., 2012)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav1.4','CACNA1F','Retina','Expressed in the Retina and Localizes at Ribbon Synapses in Cone and Rod photoreceptors','Cav L-type, α-1F subunit, Each α1 subunit consists of 6 helical transmembrane segments (S1-S6)','Synaptic Transmission and Cellular organization in Retina','Congenital Stationary Night Blindness , Syndromic Autism, Schizophrenia','(McRory et al., 2004) (Klassen et al., 2011) (Wei and Hemmings., 2006)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav2.1 (P/Q)','CACNA1A','Presynaptic Terminals Cerebellar Purkinje Cells Granule Cells,Cortex','Somato-Dendritic membranes throughout the brain','Cav P/Q-type, α-1A subunit, Each α1 subunit consists of 6 helical transmembrane segments (S1-S6)','Mediating Neurotransmitter release in the Nervous System, Postsynaptic Integration, Neuroplasticity, Neural Excitability, and Gene Transcription','Spinocerebellar Ataxia Type 6','(Llinas et al., 1992) (Mintz et al., 1992) (Chen and Piedras-Rentería., 2007)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav2.2 (N)','CACNA1B','Neuron, Retinal Ganglion cell','Multi-pass membrane protein','Cav N-type, α-1B subunit, Each α1 subunit consists of 6 helical transmembrane segments (S1-S6)','Controls Neurotransmitter Release from Neurons','Episodic Ataxia Type 2, Schizophrenia and Bipolar Disorder','(Yasuda et al., 2004) (Zhang et al., 2008)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav 2.3 ( R)','CACNA1E','Neuronal Tissues (Kidney)','Multi-Pass membrane Protein','Cav R-type, α-1E subunit, Each α1 subunit consists of 6 helical transmembrane segments (S1-S6)','Modulation of firing patterns of neurons, Muscle Contraction, Hormone or neurotransmitter release, Cell Motility, Cell Division and Cell Death','Juvenile Myoclinic Epilepsy','(Schneider et al., 1994) (Williams et al., 1994) (Suzuki et al., 2004)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav3.1','CACNA1G','Neurons and Cardiac tissue','Multi-pass membrane protein','Cav T-type, α-1G subunit, Each α1 subunit consists of 6 helical transmembrane segments (S1-S6)','Neuronal Firing Activity, Cardiac Pacemaker Activity','Epilepsy, Cardiac Hypertrophy','(Hagiwara et al., 1988) (Huguenard, JR. 1996) (Tsakiridou et al., 1995)');
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insert into Channelopedia values ('Calcium (CaV) Channel','Cav3.2','CACNA1H','Kidney, Liver, Heart, Brain','Multi-pass membrane protein','Cav T-type, α-1H subunit, Each α1 subunit consists of 6 helical transmembrane segments (S1-S6)','Secretion of Neuroendocrine Prostate Cancer Cells, Contraction, Secretion, Neurotransmission and gene Expression.','Epilepsy, Idiopathic generalized Type 6, Epilepsy, childhood absence 6 (ECA6)','(Splawski et al., 2006)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav3.3','CACNA1I','Brain Specific','Somatodendritic Compartment of many Types of Neurones','Cav T-type α- 1I subunit, Each α1 subunit consists of 6 helical transmembrane segments (S1-S6)','Electrical and Signaling, generate burst firing and Pacemaker Activity','Hyperalgesia','(Talley et al., 1999) (Carbone and Lux., 1984) (Kim et al., 2003)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav β1','CACNB1','Brain, Heart, Spleen, Central Nervous System & Neuroblastoma Cell','Sarcolemma; Peripheral membrane protein','Cav L-type, β-1 (auxiliary)subunit','Modulating G protein inhibition and controlling the alpha-1 subunit membrane targeting','Malignant Hyperthermia susceptibility ( Autosomal Dominant Disorder of Skeletal Muscle )','(Gregg et al.,1996)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav β2','CACNB2','Heart, Retina','Membrane of smooth Muscle','Cav L-type , β-2 (auxiliary) subunit','Hyperpolarizing Shifts ','Lambert-Eaton Myasthenic Syndrome, Brugada Symdrome','(Perez-Reyes et al.,1992) (Pichler et al., 1997) (Ball et al., 2002) (Reimer et al., 2000) (Singer et al., 1991)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav β4','CACNB4','Brain, predominantly in the Cerebellum, Kidney','Vestibular, Cerebellar Neuronal membrane','Cav L-type , β-4 (auxiliary) subunit','Shifting the Voltage dependencies of activation and inactivation, Modulating G protein inhibition','Idiopathic generalized Epilepsy, Juvenile Myoclonic Epilepsy','(Xu et al., 2011) (Ohmori et al., 2008)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav Y2','CACNG2','Brain','Multi-pass membrane protein','Cav Y-2 (auxiliary) subunit','Regulates the trafficking and gating properties of AMPA-selective glutamate receptors','Mental Retardation','(Hamdan et al., 2011) (Shi et al., 2010) (Black and Lennon., 1999)');
insert into Channelopedia values ('Calcium (CaV) Channel','Cav Y5','CACNG5','Epithelia','Cell Junction , Postsynaptic Cell Membrane','Cav Y-5 (auxiliary) subunit','Modulates gating properties','Schizophrenia and Bipolar Disorder','(Chen RS. et al., 2007) (Curtis et al., 2011) (Chu et al., 2001)');
insert into Channelopedia values ('Chloride (Clv) Channel','ClvC1','CLCN1','Predominantly expressed in Skeletal Muscles','Multi-pass membrane protein','ClvC Type -1. Homodimer. Each monomer consist of 18 helical segments','Membrane potential stabilization, Signal Transduction and Transepithelial Transport','Autosomal Recessive Myotonia Congenita','(Koch et al., 1992) (George et al., 1993) (Lorenz et al., 1994)');
insert into Channelopedia values ('Chloride (Clv) Channel','ClvC2','CLCN2','Skeletal Muscle','Multi-pass membrane protein','ClvC Type -2. Homodimer. Each monomer consist of 18 helical segments,','Homeostasis in various Cells','Susceptibility to Epilepsy, Idiopathic generalized, Myoclonic Jerks','(Saint-Martin et al., 2009) (Lamb et al., 1999) (Jeworutzki et al., 2012)');
insert into Channelopedia values ('Chloride (Clv) Channel','ClvC3','CLCN3','Coronary Vascular Smooth Muscle Cells and Expressed at a Low level in Aortic Endothelial Cells','Multi-pass membrane protein','ClvC Type -3 ,Homo- or heterodimer. Each monomer consist of 18 helical segments','Neuronal cells to establish short-term Memory, Myoclonic Jerks','Juvenile absence Epilepsy Type 2, Idiopathic generalized Epilepsy','(Cid et al., 1995) (Lamb et al., 1999)');
insert into Channelopedia values ('Chloride (Clv) Channel','ClvC6','CLCN6','Testis, Ovary, Small intestine, Brain and Skeletal Muscle','Endosome membrane','_____','Antiporter and Contributes to the Acidification of the Lysosome Lumen','Lysosomal storage disease','(Ota et al., 2004) (Brandt and Jentsch., 1995) (Eggermont et.al., 1997) (Lamb et al., 1999) (Ignoul et al., 2007) (Poet et al., 2006)');
insert into Channelopedia values ('Chloride (Clv) Channel','ClvC7','CLCN7','Brain, Testis, Muscle and Kidney','Lysosome membrane, Multi-pass membrane protein','ClvC Type -7. Heteromers of α -(CLCN7) and β-(OSTM1) subunits','Antiporter and Contributes to the Acidification of the Lysosome Lumen','Infantile Malignant, Osteopetrosis Type 2, Albers-Schonberg, Disease or Marble Disease ','(Schroeder et al., 2007) (Graves et al., 2008) (Leisle et.al., 2011) (Kornak et al., 2001)');
insert into Channelopedia values ('Chloride (Clv) Channel','ClCa1','CLCA1','Small Intestine, Colon, Goblet Cells Testis and Kidney','Localized to Microvilli, Basal Crypt Epithelia, Peripheral membrane protein; Extracellular side','_____','Goblet cell, Metaplasia, Mucus Hypersecretion, Cystic Fibrosis and AHR','Biomarker in Chronic Asthma, Chronic Obstructive Pulmonary Disease','(Gruber et al., 1998) (Bustin et al., 2001) (Hoshino et al., 2002) (Toda et al.,2002) (Lee et al., 2005) (Gibson et al., 2005)');
insert into Channelopedia values ('Chloride (Clv) Channel','ClCa2','CLCA2','Epithelium including Cornea, Esophagus, Larynx','Single-pass type I membrane protein. Basal cell membrane; Single-pass type I membrane protein','_____','May act as a Tumor suppressor in Breast and Colorectal Cancer, Cell Adhesion','Leukemia, Breast Tumor Suppressor Gene','(Gruber et al., 1999) (Bustin et al., 2001) (Abdel-Ghany et al., 2001) (Connon et al., 2005) (Connon et al., 2006)');
create table Reference (Complete_Reference nvarchar(MAX));
insert into Reference values ('Bendahhou, S; Cummins, TR; Kula, RW; Fu, YH; Ptácek, LJ. (2002). Impairment of slow inactivation as a common mechanism for periodic paralysis in DIIS4-S5. Neurology.58(8), 1266-1272.');
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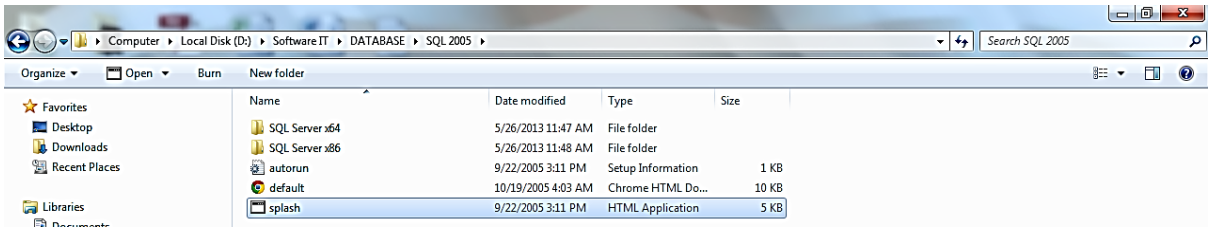
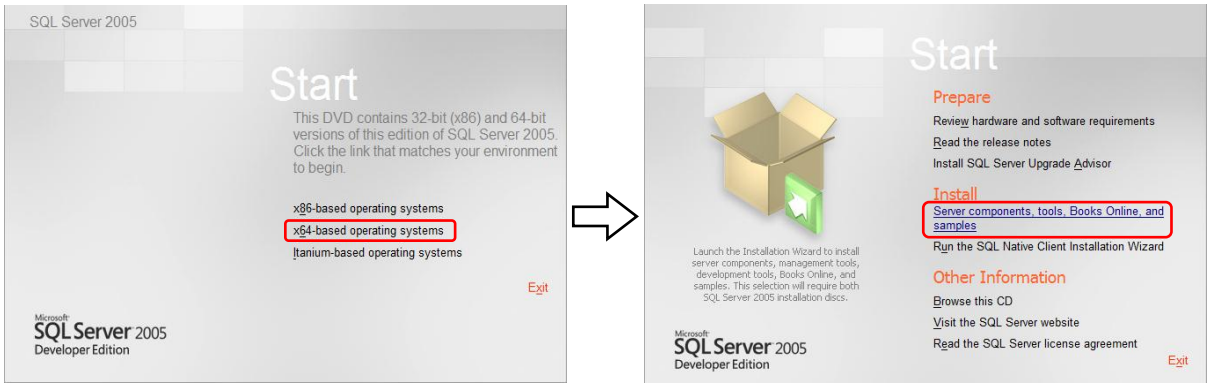
4.3 Installation of 'Neurological Channelopathic Knowledge Base (NCKB) Software' into another computer:

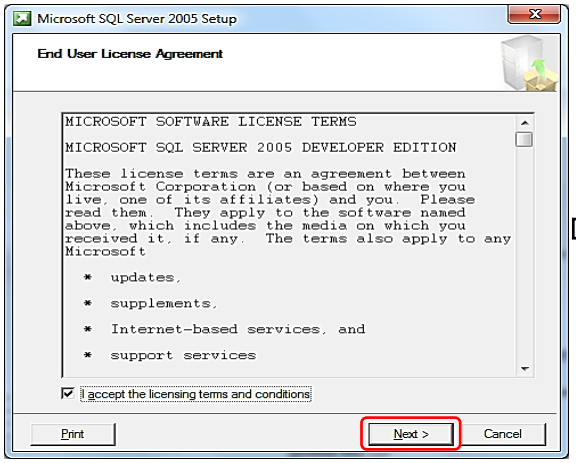
a. Install SQL Server Management Studio 2005 Setup.
b. Loading of database into computer
c. Install Neurological Channelopathic Knowledge Base (NCKB) Setup.

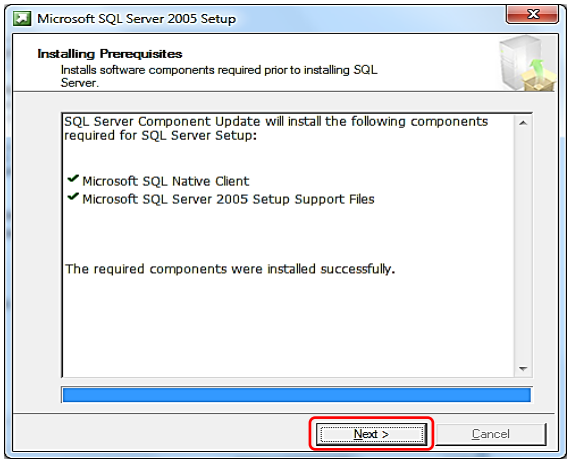
a. Installation of SQL Server Management studio 2005:

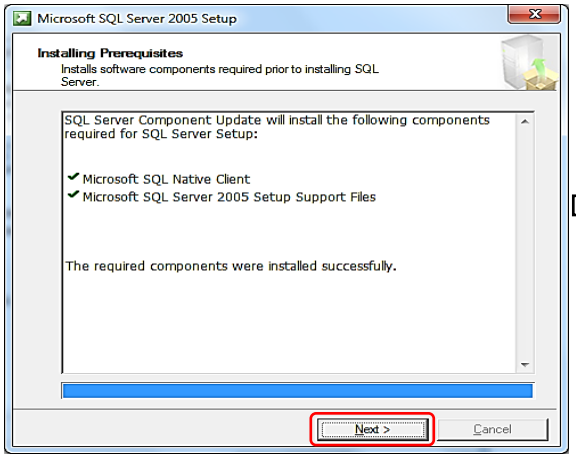
i. Open 'SQL 2005' folder and click on 'splash'.






Microsoft SQL Server 2005 Setup
End User License Agreement
MICROSOFT SOFTWARE LICENSE TERMS
MICROSOFT SQL SERVER 2005 DEVELOPER EDITION
These license terms are an agreement between Microsoft Corporation (or based on where you live, one of its affiliates) and you. Please read them. They apply to the software named above, which includes the media on which you received it, if any. The terms also apply to any Microsoft
* updates,
* supplements,
* Internet-based services, and
* support services
I accept the licensing terms and conditions.
Print
Next >
Cancel


Microsoft SQL Server 2005 Setup
Installing Prerequisites
Installs software components required prior to installing SQL Server.
SQL Server Component Update will install the following components required for SQL Server Setup:
Microsoft SQL Native Client
Microsoft SQL Server 2005 Setup Support Files
The required components were installed successfully.
Next >
Cancel


Microsoft SQL Server 2005 Setup
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Microsoft SQL Native Client
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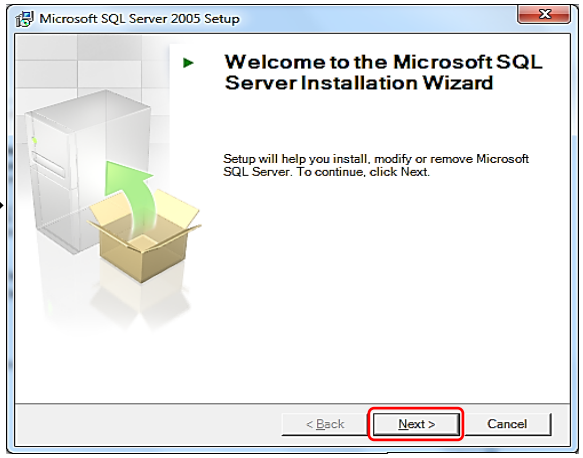
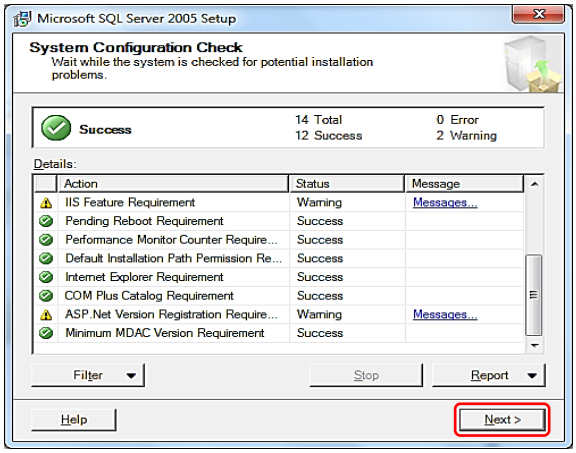
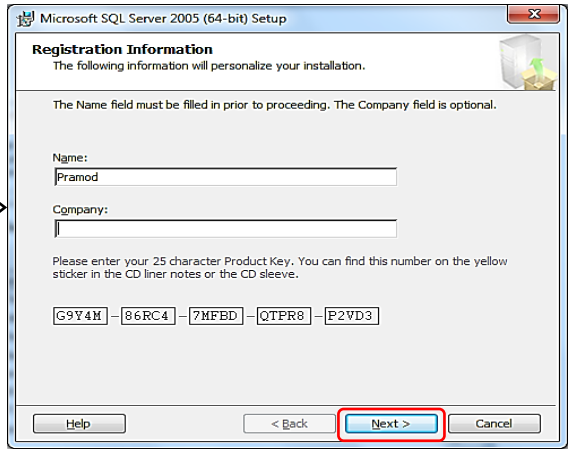
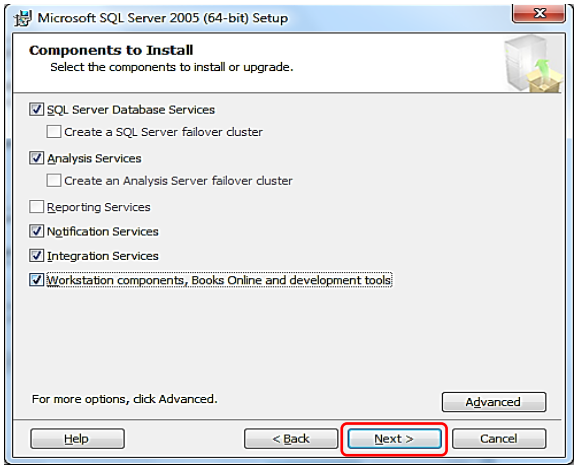
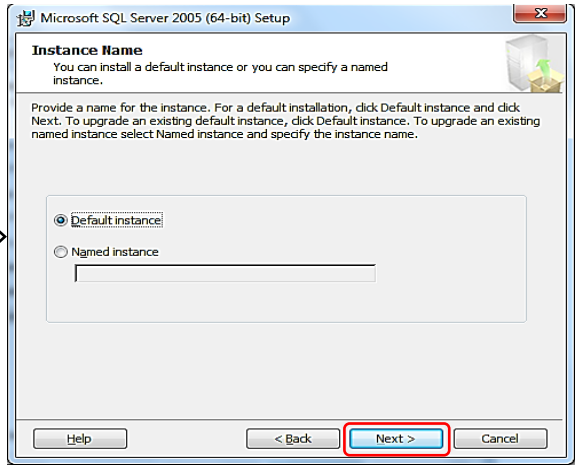
The required components were installed successfully.
Next >
Cancel

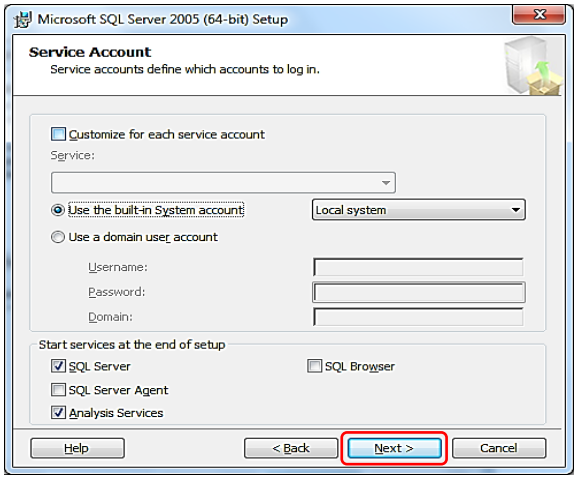

Microsoft SQL Server 2005 Setup
Welcome to the Microsoft SQL Server Installation Wizard
Setup will help you install, modify or remove Microsoft SQL Server. To continue, click Next.
< Back
Next >
Cancel

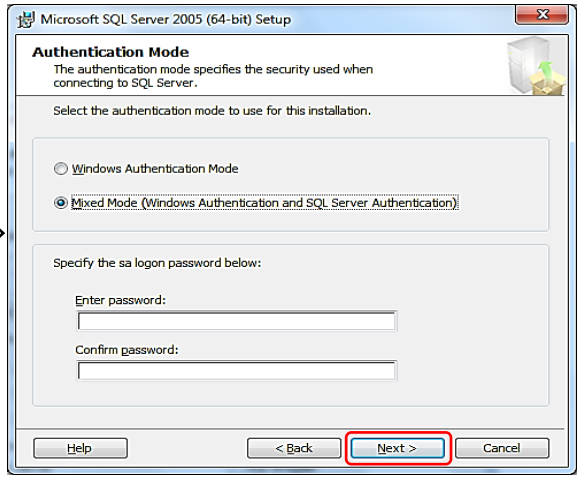

Microsoft SQL Server 2005 Setup
System Configuration Check
Wait while the system is checked for potential installation problems.
Success
14 Total
12 Success
0 Error
2 Warning
Details:
Action
Status
Message
IIS Feature Requirement
Warning
Messages...
Pending Reboot Requirement
Success
Performance Monitor Counter Require...
Success
Default Installation Path Permission Re...
Success
Internet Explorer Requirement
Success
COM Plus Catalog Requirement
Success
ASP.Net Version Registration Require...
Warning
Messages...
Minimum MDAC Version Requirement
Success
Filter
Stop
Report
Help
Next >

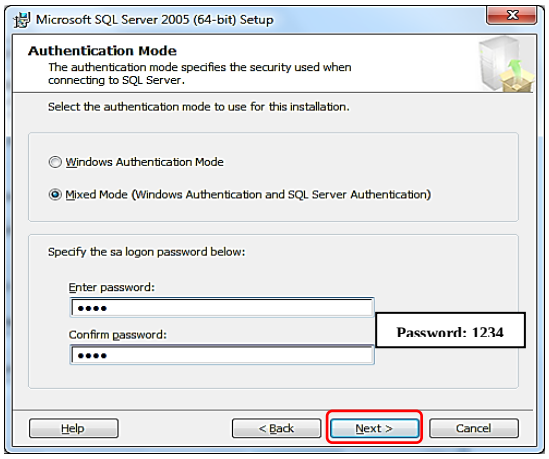

Microsoft SQL Server 2005 (64-bit) Setup
Registration Information
The following information will personalize your installation.
The Name field must be filled in prior to proceeding. The Company field is optional.
Name:
Pramod
Company:
Please enter your 25 character Product Key. You can find this number on the yellow sticker in the CD liner notes or the CD sleeve.
G9Y4M - 86RC4 - 7MFBD - QTPR8 - P2VD3
Help
< Back
Next >
Cancel

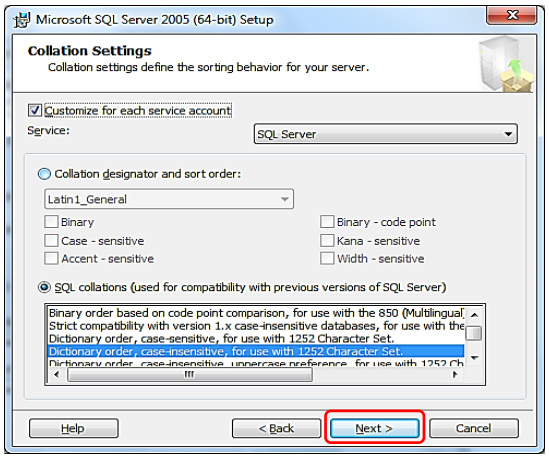

Microsoft SQL Server 2005 (64-bit) Setup
Components to Install
Select the components to install or upgrade.
SQL Server Database Services
Create a SQL Server failover cluster
Analysis Services
Create an Analysis Server failover cluster
Reporting Services
Notification Services
Integration Services
Workstation components, Books Online and development tools
For more options, click Advanced.
Advanced
Help
< Back
Next >
Cancel

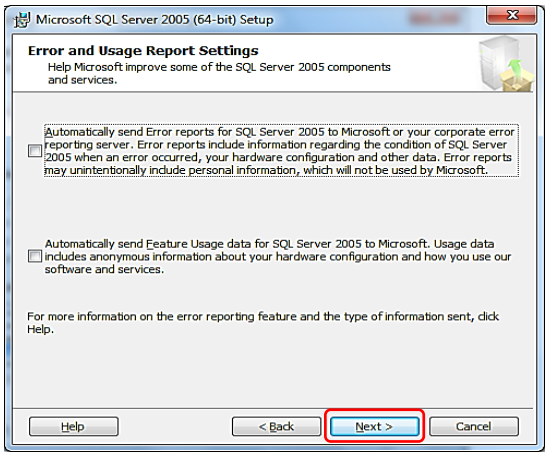

Microsoft SQL Server 2005 (64-bit) Setup
Instance Name
You can install a default instance or you can specify a named instance.
Provide a name for the instance. For a default installation, click Default instance and click Next. To upgrade an existing default instance, click Default instance. To upgrade an existing named instance select Named instance and specify the instance name.
Default instance
Named instance
Help
< Back
Next >
Cancel

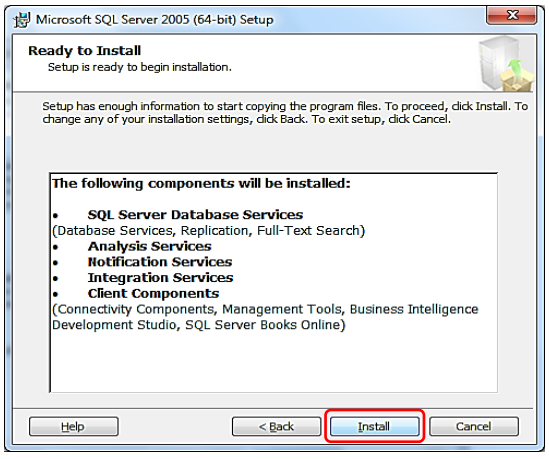

Microsoft SQL Server 2005 (64-bit) Setup
Service Account
Service accounts define which accounts to log in.
Customize for each service account
Service:
Use the built-in System account
Local system
Use a domain user account
Username:
Password:
Domain:
Start services at the end of setup
SQL Server
SQL Browser
SQL Server Agent
Analysis Services
Help
< Back
Next >
Cancel

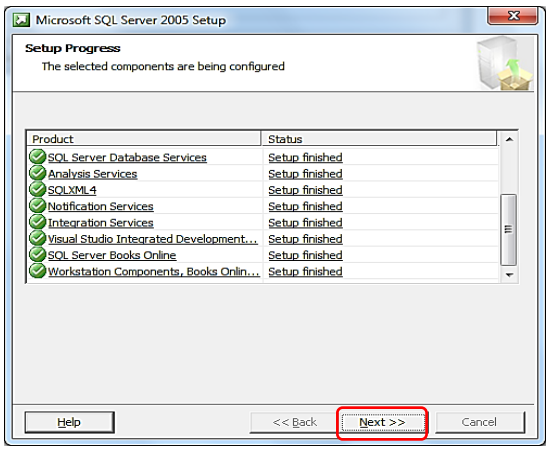

Microsoft SQL Server 2005 (64-bit) Setup
Authentication Mode
The authentication mode specifies the security used when connecting to SQL Server.
Select the authentication mode to use for this installation.
Windows Authentication Mode
Mixed Mode (Windows Authentication and SQL Server Authentication)
Specify the sa logon password below:
Enter password:
Confirm password:
Help
< Back
Next >
Cancel

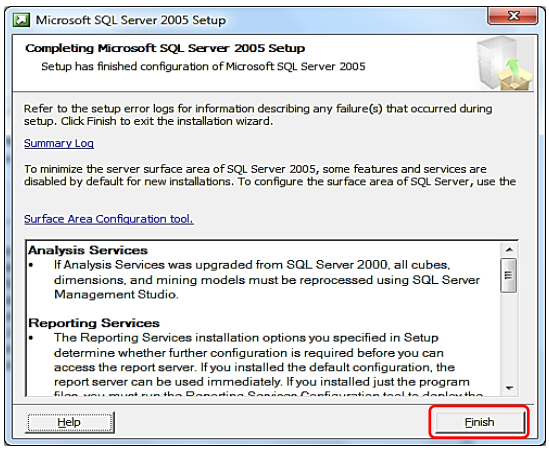

Microsoft SQL Server 2005 (64-bit) Setup
Authentication Mode
The authentication mode specifies the security used when connecting to SQL Server.
Select the authentication mode to use for this installation.
Windows Authentication Mode
Mixed Mode (Windows Authentication and SQL Server Authentication)
Specify the sa logon password below:
Enter password:
Confirm password:
Password: 1234
Help
< Back
Next >
Cancel


Microsoft SQL Server 2005 (64-bit) Setup
Collation Settings
Collation settings define the sorting behavior for your server.
Customize for each service account
Service:
SQL Server
Collation designator and sort order:
Latin1_General
Binary
Binary - code point
Case - sensitive
Kana - sensitive
Accent - sensitive
Width - sensitive
SQL collations (used for compatibility with previous versions of SQL Server)
Binary order based on code point comparison, for use with the 850 (Multilingual)
Strict compatibility with version 1.x case-insensitive databases, for use with the
Dictionary order, case-sensitive, for use with 1252 Character Set.
Dictionary order, case-insensitive, for use with 1252 Character Set
Help
< Back
Next >
Cancel


Microsoft SQL Server 2005 (64-bit) Setup
Error and Usage Report Settings
Help Microsoft improve some of the SQL Server 2005 components and services.
Automatically send Error reports for SQL Server 2005 to Microsoft or your corporate error reporting server. Error reports include information regarding the condition of SQL Server 2005 when an error occurred, your hardware configuration and other data. Error reports may unintentionally include personal information, which will not be used by Microsoft.
Automatically send Feature Usage data for SQL Server 2005 to Microsoft. Usage data includes anonymous information about your hardware configuration and how you use our software and services.
For more information on the error reporting feature and the type of information sent, click Help.
Help
< Back
Next >
Cancel


Microsoft SQL Server 2005 (64-bit) Setup
Ready to Install
Setup is ready to begin installation.
Setup has enough information to start copying the program files. To proceed, click Install. To change any of your installation settings, click Back. To exit setup, click Cancel.
The following components will be installed:
SQL Server Database Services
(Database Services, Replication, Full-Text Search)
Analysis Services
Notification Services
Integration Services
Client Components
(Connectivity Components, Management Tools, Business Intelligence Development Studio, SQL Server Books Online)
Help
< Back
Install
Cancel


Microsoft SQL Server 2005 Setup
Setup Progress
The selected components are being configured
Product
Status
SQL Server Database Services
Setup finished
Analysis Services
Setup finished
SQLXML4
Setup finished
Notification Services
Setup finished
Integration Services
Setup finished
Visual Studio Integrated Development...
Setup finished
SQL Server Books Online
Setup finished
Workstation Components, Books Onlin...
Setup finished
Help
<< Back
Next >>
Cancel

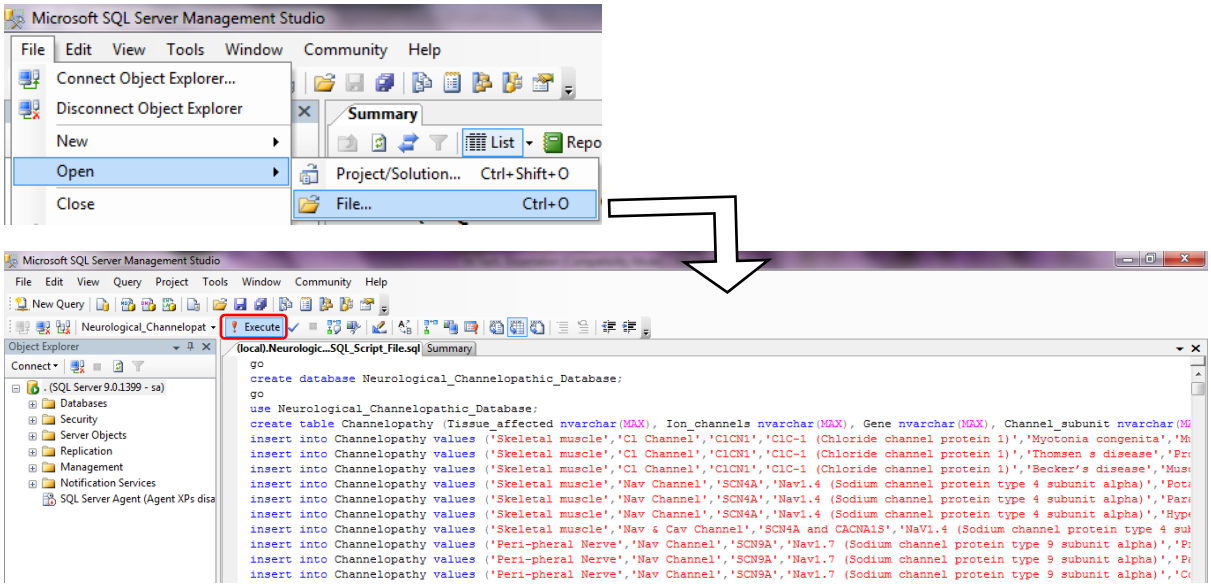

Microsoft SQL Server 2005 Setup
Completing Microsoft SQL Server 2005 Setup
Setup has finished configuration of Microsoft SQL Server 2005
Refer to the setup error logs for information describing any failure(s) that occurred during setup. Click Finish to exit the installation wizard.
Summary Log
To minimize the server surface area of SQL Server 2005, some features and services are disabled by default for new installations. To configure the surface area of SQL Server, use the
Surface Area Configuration tool.
Analysis Services
If Analysis Services was upgraded from SQL Server 2000, all cubes, dimensions, and mining models must be reprocessed using SQL Server Management Studio.
Reporting Services
The Reporting Services installation options you specified in Setup determine whether further configuration is required before you can access the report server. If you installed the default configuration, the report server can be used immediately. If you installed just the program
Help
Finish

b. Loading of database into computer:

i. Launch ‘Microsoft SQL Server Management Studio 2005’

ii. Open ‘NCKB_SQL_Sript_File’ and execute it by clicking on ‘Execute’ or pressing ‘F5’.

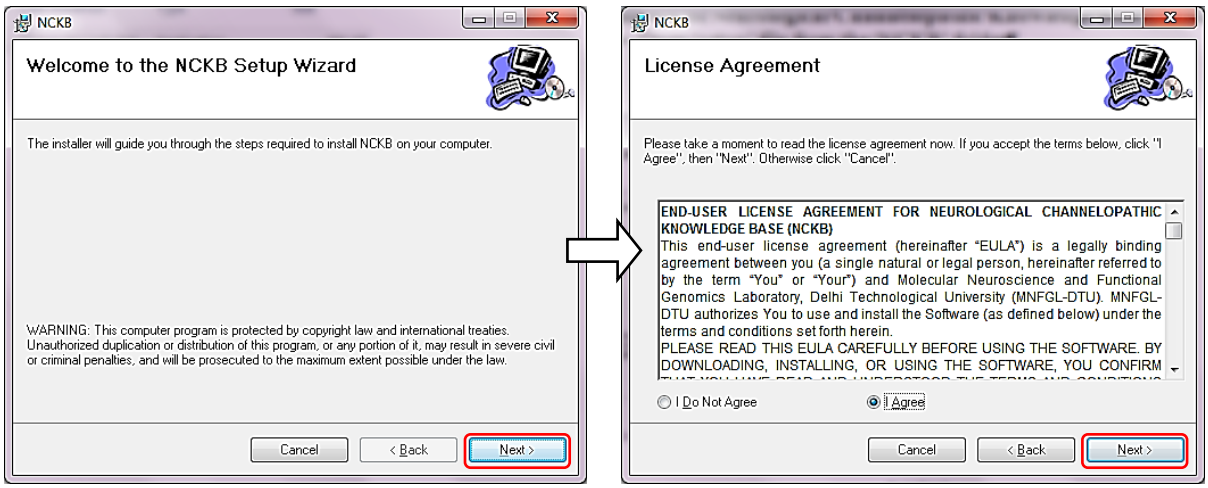
- Click on File→ Open→ File
- Select ‘NCKB_SQL_Script_File’ and Open
- Click on ‘Execute’ or Press ‘F5’

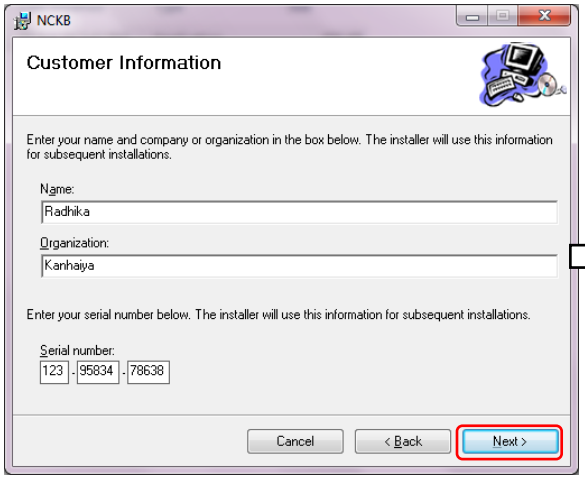


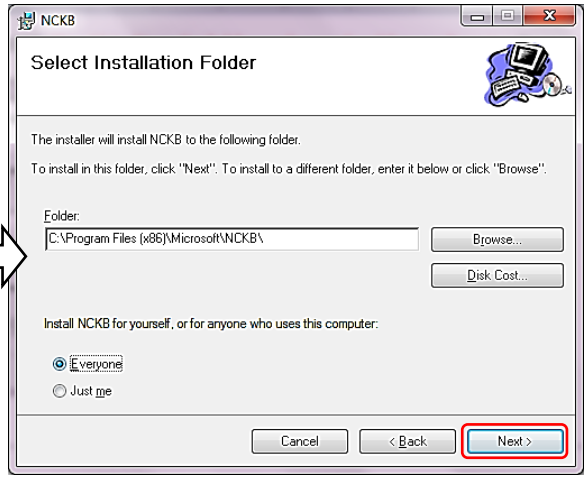
c. Installation of Neurological Channelopathic Knowledge Base (NCKB) Setup

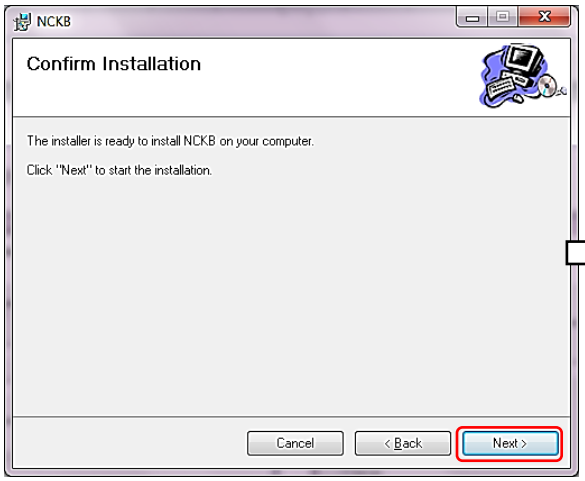
i. Open ‘setup’ file from the ‘NCKB’ folder

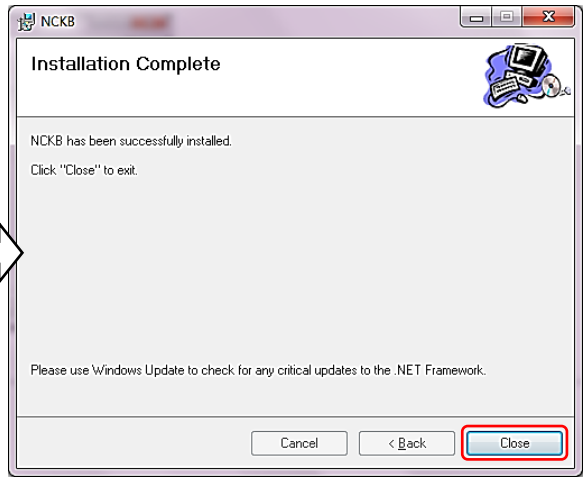
- NCKB → NCKB → Debug → setup




NCKB
Customer Information
Enter your name and company or organization in the box below. The installer will use this information for subsequent installations.
Name:
Radhika
Organization:
Kanhaiya
Enter your serial number below. The installer will use this information for subsequent installations.
Serial number:
123 - 95834 - 78638
Cancel
< Back
Next >

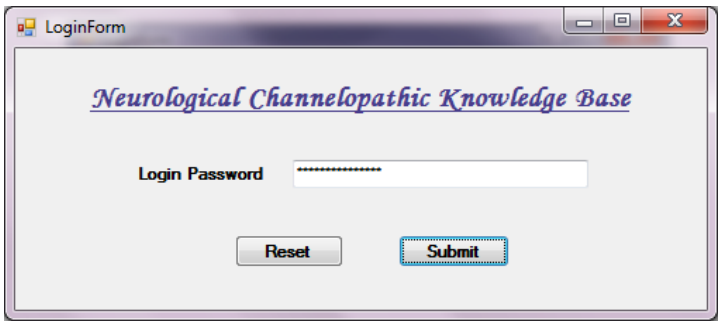

NCKB
Select Installation Folder
The installer will install NCKB to the following folder.
To install in this folder, click "Next". To install to a different folder, enter it below or click "Browse".
Folder:
C:\Program Files (x86)\Microsoft\NCKB\
Browse...
Disk Cost...
Install NCKB for yourself, or for anyone who uses this computer:
Everyone
Just me
Cancel
< Back
Next >


NCKB
Confirm Installation
The installer is ready to install NCKB on your computer.
Click "Next" to start the installation.
Cancel
< Back
Next >


NCKB
Installation Complete
NCKB has been successfully installed.
Click "Close" to exit.
Please use Windows Update to check for any critical updates to the .NET Framework.
Cancel
< Back
Close

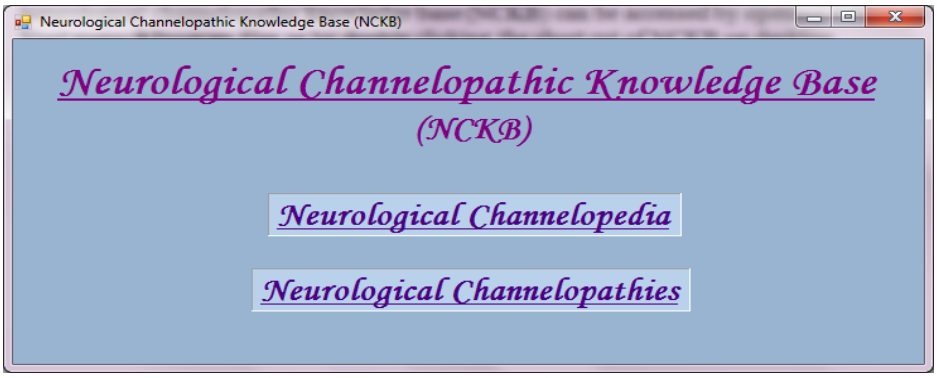
RESULTS

Neurological channelopathic knowledge base (NCKB) can be accessed by opening it through Start menu→Program files or by double clicking the short cut of NCKB on desktop.
Login form has been opened where Login Password has been entered 'KnowledgeBase4U'.

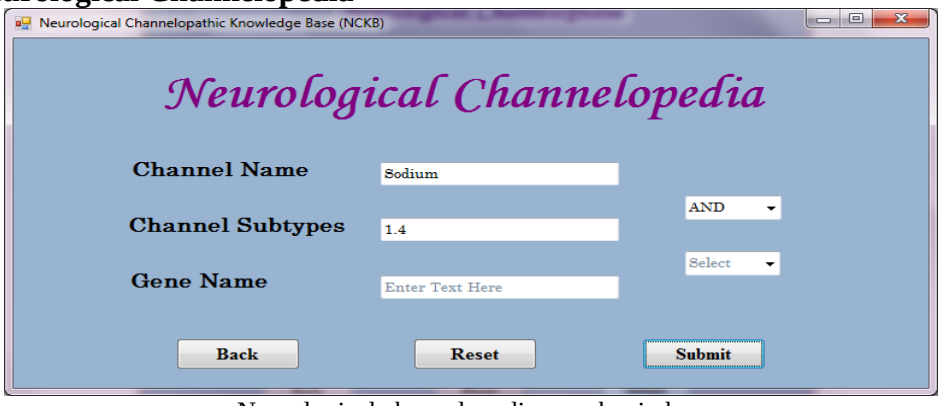


There were two links for database searching depending on the requirement.

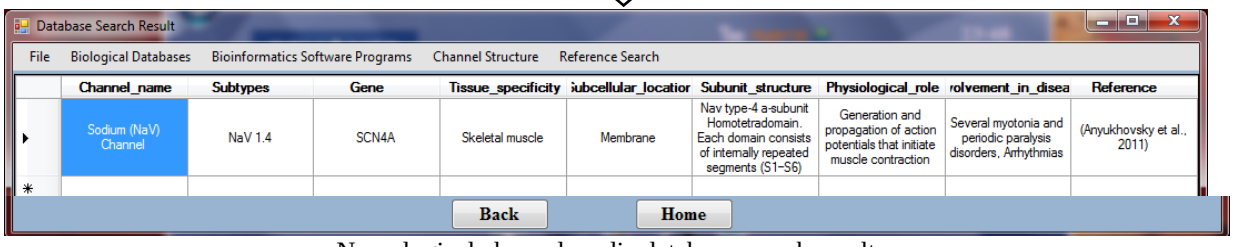
a. Neurological Channelopedia
b. Neurological Channelopathies



a. Neurological Channelopedia

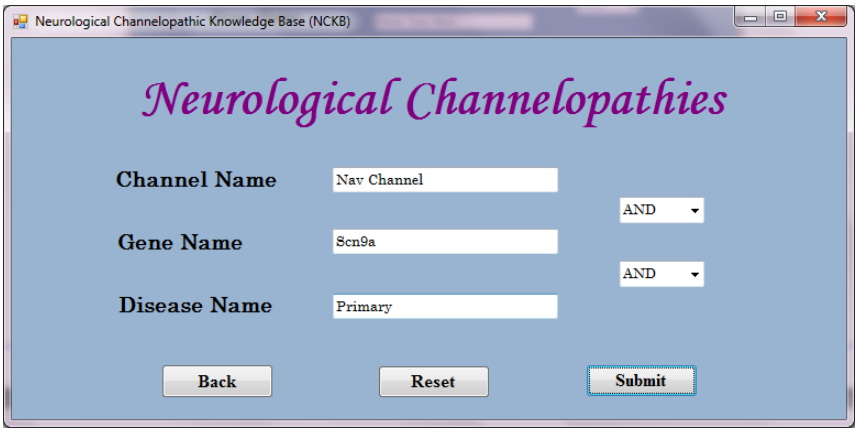


Neurological channelopedia search window

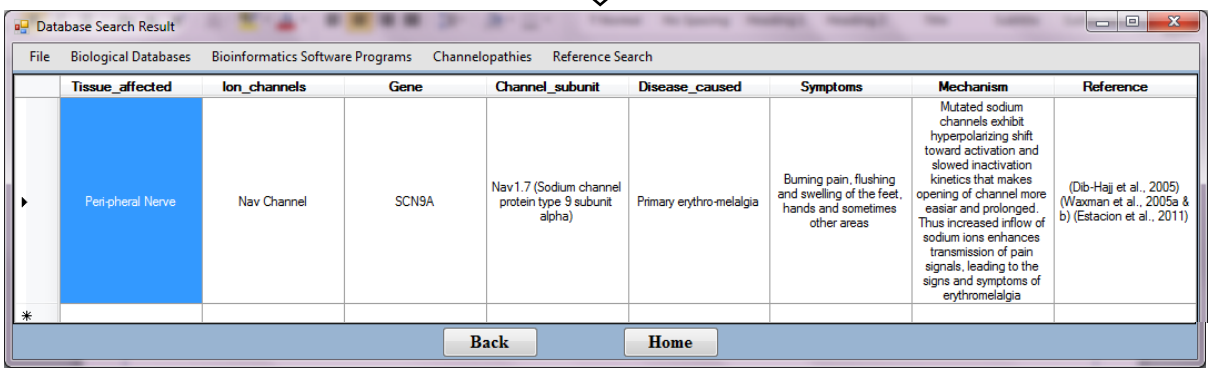


Neurological channelopedia database search result

b. Neurological Channelopathies



Neurological channelopathies search window



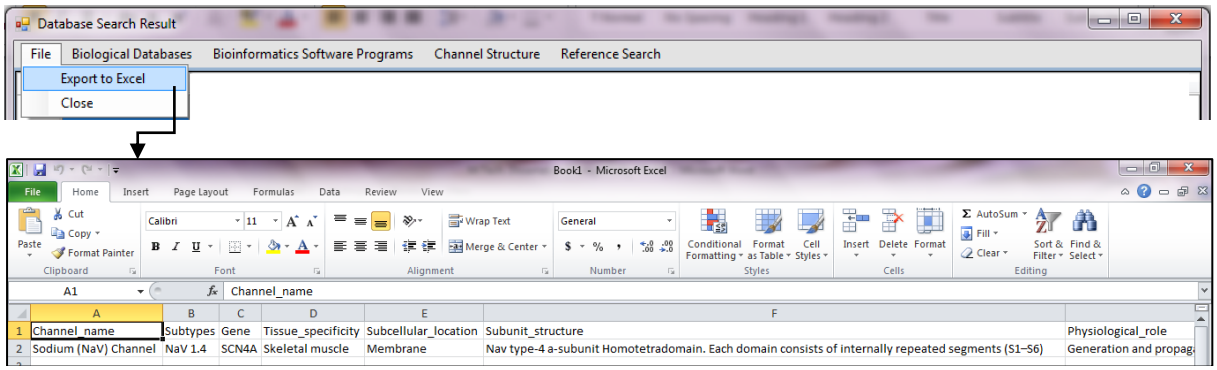
Neurological channelopathies database search result

✓ **Menu Bar Items:**

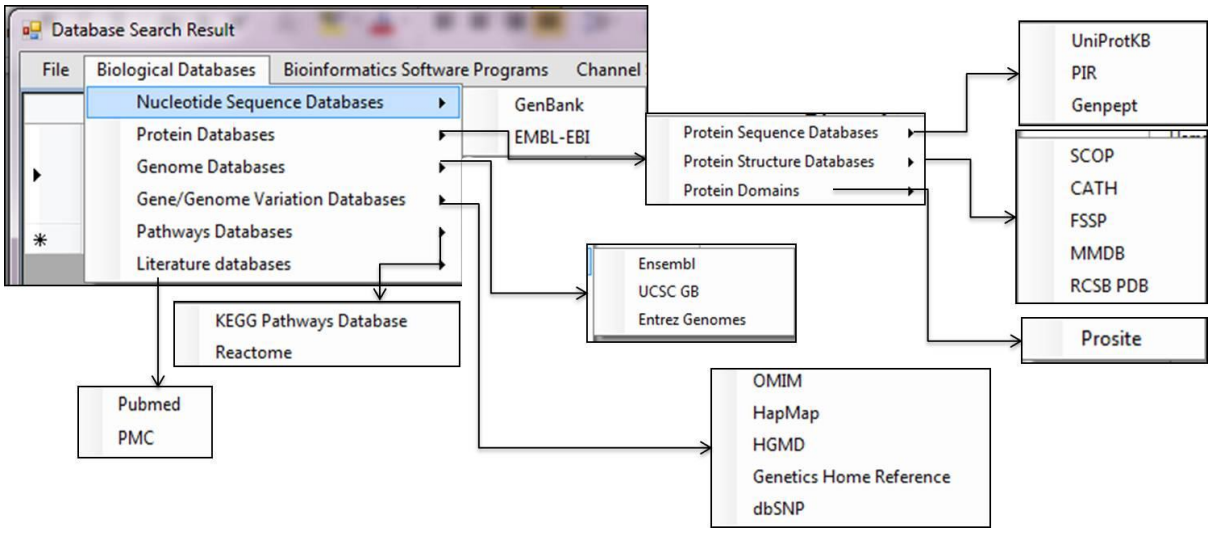
Menu bar items contain the tools required for accessing the software. It has following items

1. File
2. Biological Databases
3. Bioinformatics Software Programs
4. Channel Structure
5. Channelopathies
6. Reference Search

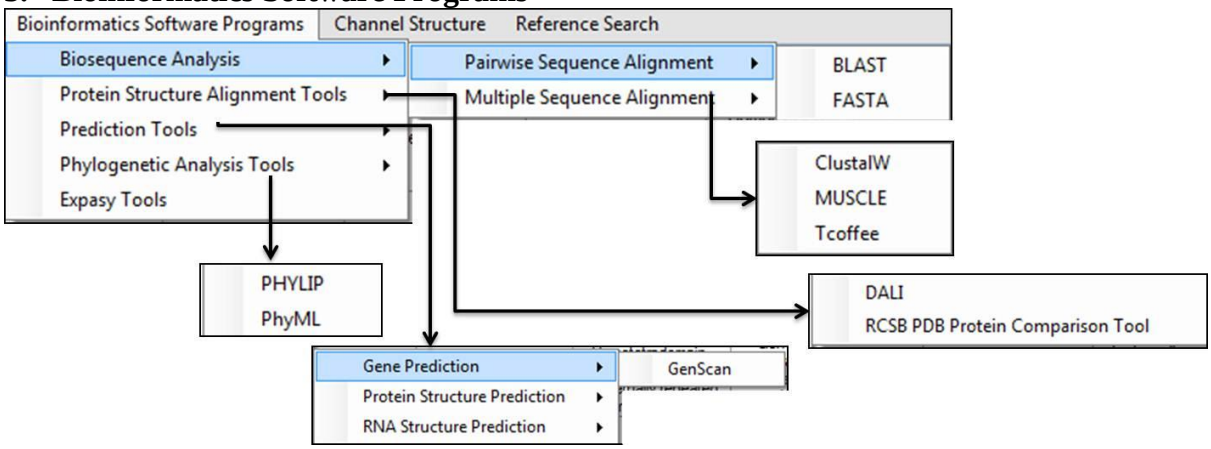
1. File→ Export to Excel



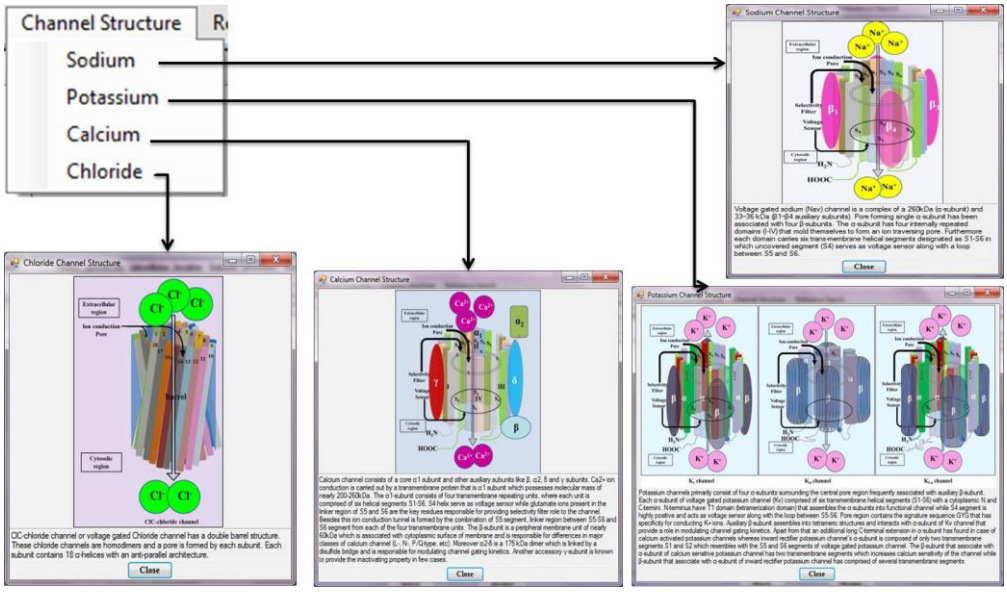
2. Biological Databases



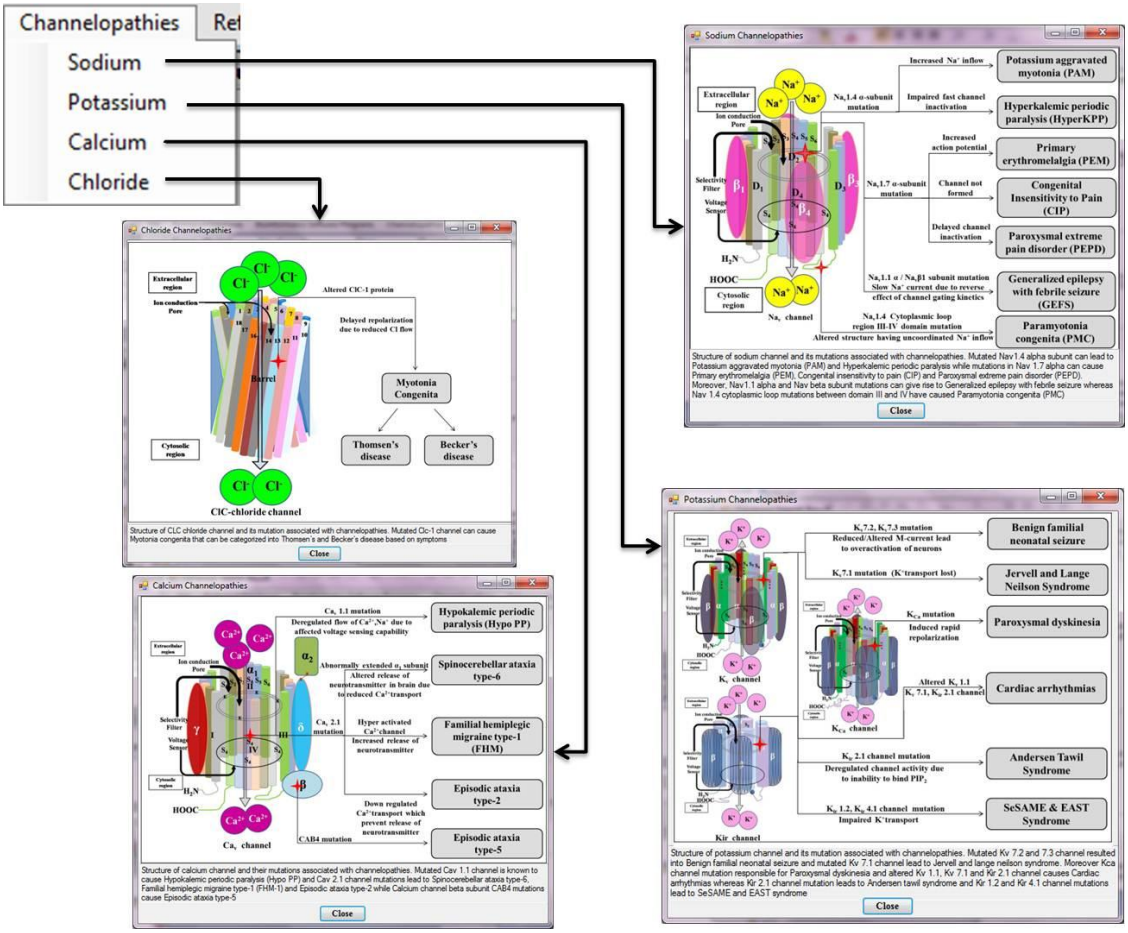
3. Bioinformatics Software Programs



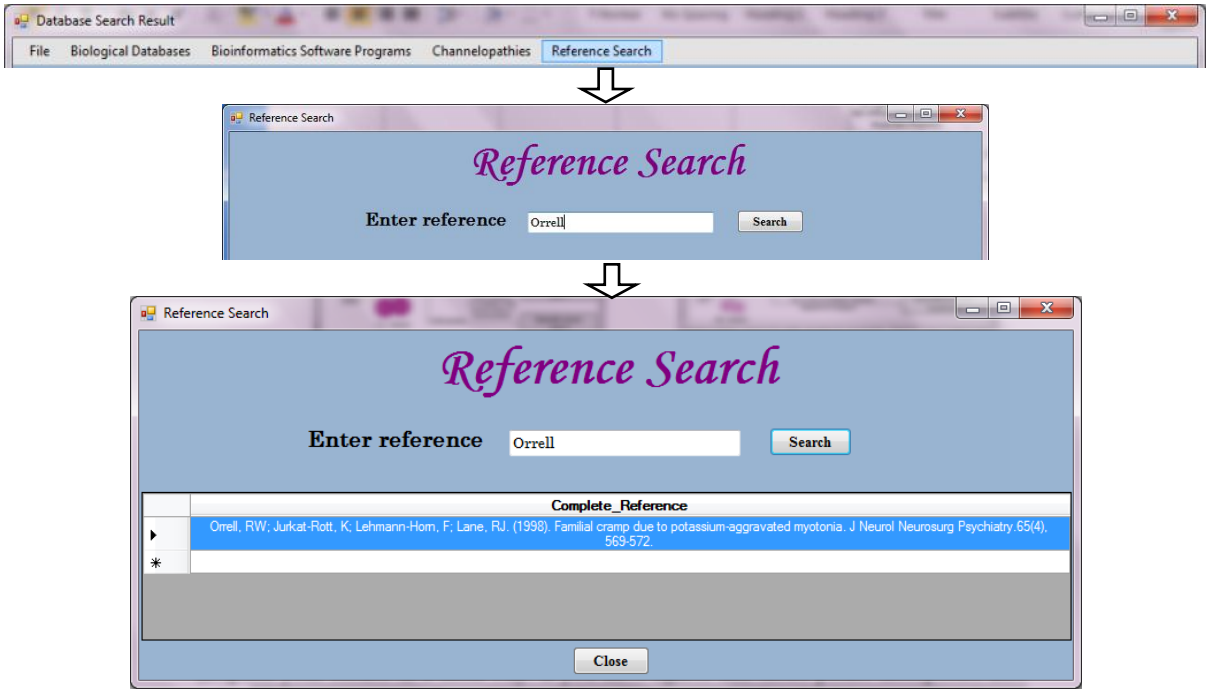
4. Channel Structure



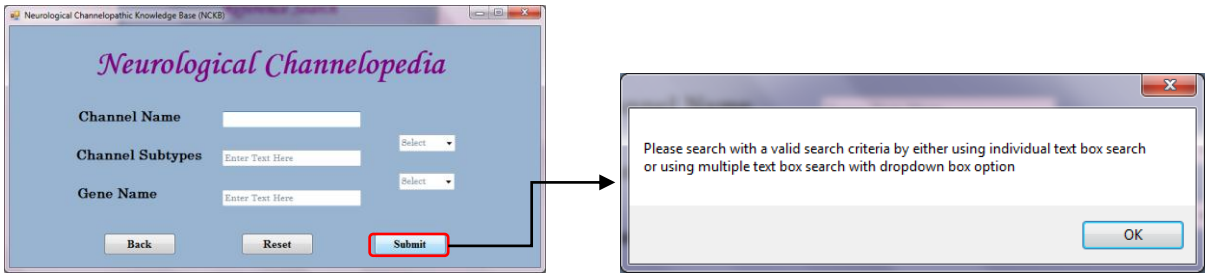
5. Channelopathies

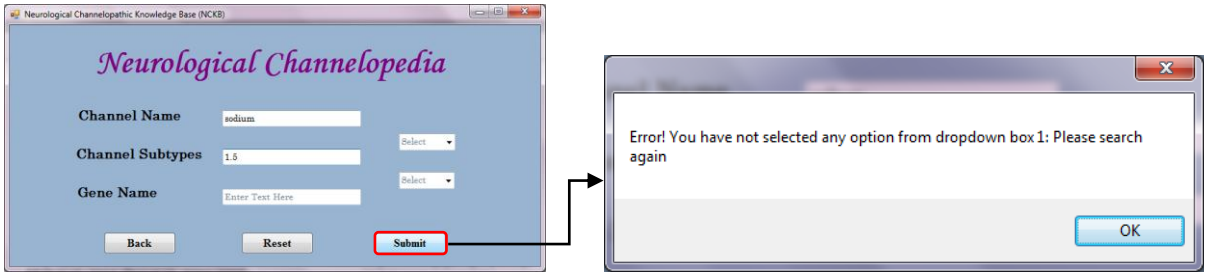


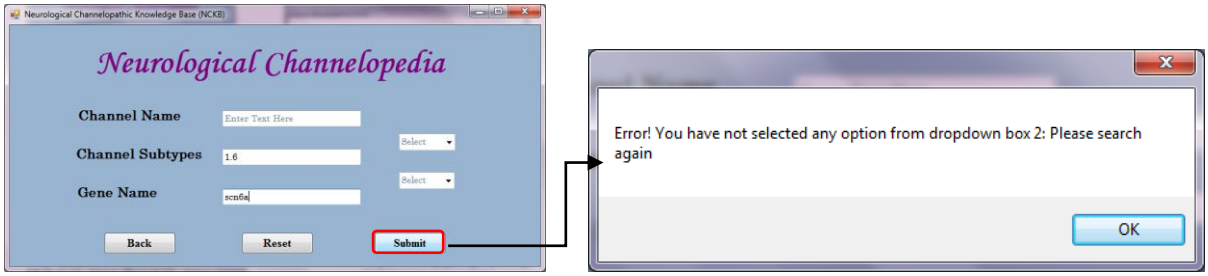
6. Reference Search

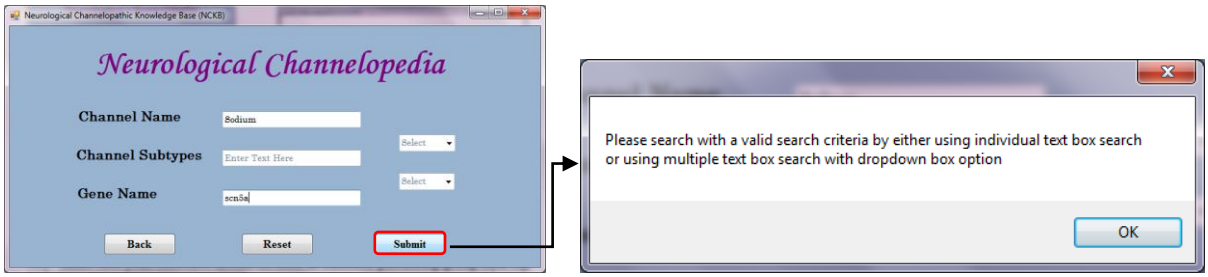


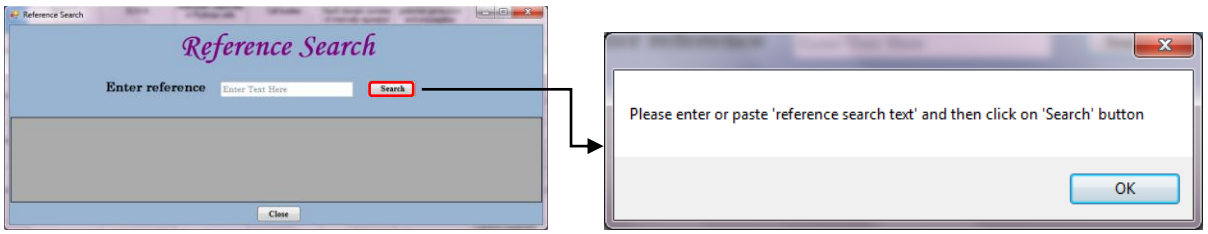
✓ **Exception Handling:**
Exceptions have been handled with the help of 'Message Box' that will display the error message.











DISCUSSION AND FUTURE PERSPECTIVE

Databases, like journals are the crucial element of our research pursuits. Neurological Channelopathic Knowledge Base (NCKB) has been serving the purpose of central repository for Ion channels and Neurological channelopathies. It is a visual studio based user interface programmed software that mediates suitable data retrieval using SQL programming. It has been designed with the help of two software that involves 'SQL Server Management Studio 2005' and 'Microsoft Visual Studio 2008'. NCKB contains two databases that are Neurological Channelopedia and Neurological Channelopathies. Neurological Channelopedia possess information about the ion channels while Neurological channelopathic database stores the genetic, structural and mechanistic information about the channelopathies. NCKB has been coded with Structural query language as well as C# (sharp). NCKB has been supplemented with the online available bioinformatic tools that can be accessed from here. Another interesting feature is its exceptional security that underlies at three levels. One at NCKB software installation in form of a 'Product Key', another at software access in form of 'Login Password' and finally at the database installation in the form of 'SQL connection password'. Moreover exceptions have been handled with care that identified the absolute error involved. Last but not the least; it is a user friendly single handed software with portability.

One of the most important future perspectives involves the biocuration of vast biological heterogeneous data. Major challenge for biocurators is to develop the innovative methods to capture, analyse and presentation of biological data. High computational analytical tools are going to be the area of interest for the researchers along with the well established data. Database integrity with the analytical tools is the essential domain for recent database developers. NCKB possess all the features mentioned before. Here for the purpose of sharing of biological information, designing of web based applications have significant necessity that can be designed with the help of high definition language based java programming provide suitable user interface.

REFERENCES

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APPENDIX

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