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Research Article

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Protein-protein interaction study associated with epilepsy and migraine

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Abstract

Epilepsy is a chronic non-communicable disease with symptoms of recurrent episodes of uncontrolled movements of body with associated loss of consciousness with loss of bowel/bladder function. Two significant proteins involved with the disease namely-Sodium channel protein type I subunit alpha, Calcium-activated potassium channel alpha-1 were taken for study.Migraine is a common neurological disease that causes a variety of symptoms notably headache-throbbing/pulsating type which gets worsened on physical activity, light, sound, smell. Two significant proteins involved with the causation of disease namely-Voltage-dependent P/Q-type calcium channel subunit alpha 1-A, Sodium/potassium-transporting ATPase subunit alpha-2 were taken for this study.The primary, secondary and tertiary structure for the proteins SCN1A_HUMAN, KCMA1_HUMAN, CAC1A_HUMAN and AT1A2_HUMAN were predicted. The sequence alignment and evolutionary relationships of the above 4 proteins of interest associated with epilepsy and migraine were interpreted. The possibilities of protein-protein interaction amongst the proteins of interest in this project wereanalyzed and the results are interpreted.

Keywords: Epilepsy, Migraine, Calcium activated potassium channel, Sodium channel, voltage dependent P/Q type calcium channel, sodium potassium- transporting ATPase.

Introduction

Epilepsy is basically a CNS disorder in which the brain activity becomes abnormal, causing seizures or episodic unusual behavior like ataxia, loss of sensation, fit like movements and even memory loss. Seizure symptoms varies with each individual which may include staring blankly for a few seconds during the episode to uncontrolled repeated twitching of extremities. Epilepsy is mostly considered to occur by a defect in neurological signaling in the brain.[1]Migraine is yet another neurological disease which is extremely incapacitatingan individual. The neurological symptoms include severe throbbing recurring pain mostly localized to one side of the head, and in a hand few of cases, both sides are affected. Attacks are often accompanied with any of the following symptoms: visual disturbances, nausea, vomiting, dizziness, sensitivity to sound, light, touch, smell, a tingling/numbness in the extremities or face. About a quarter percentile of the sufferers have a visual sign called an aura, which usually lasts less than an hour prior to the onset of the episode. In 15-20% of cases, the neurological symptoms occur before the actual headache. Typically an episode may last between 4 and 72 hours.[2]

Materials and Methods

Uniprot Database:

UniProt is a freely accessible database of protein sequence and functional information, many entries being derived from genome sequencing projects. It contains a large amount of information about the biological function of proteins derived from the research literature. The FASTA sequence of the protein of interest was retrieved using this tool. The FASTA sequence of the 4 proteins of interest was retrieved using this tool.

The UniprotKB IDs for the proteins of study are:
Sodium channel protein type 1 subunit alphaUniprotKB ID - SCN1A_HUMAN(P35498) (Epilepsy);

Calcium-activated potassium channel subunit alpha-1-UniprotKB ID- KCMA1_HUMAN (Q12791)-(Epilepsy);

Voltage-dependent P/Q-type calcium channel subunit alpha-1AUniprotKB ID- CAC1A_HUMAN(O00555) (migraine)

Sodium/potassium-transporting ATPase subunit alpha-2-UniprotKB ID- AT1A2_HUMAN(P50993) (migraine)

Protparam:

The physic-chemical parameters like molecular weight, theoretical pI, amino acid composition, extinction coefficient of the protein sequence are obtained from the ProtparamDatabase.[4] Primary structures for the proteins were obtained using the input raw sequence obtained from the Uniprot

SOPMA Database:

SOPMA Database is used to obtain the secondary structure of the proteins such as helix(H), extended beta strand (E) and coil (C) and also the probability values for each secondary structure at each amino acid position.[5] Secondary structures or the 2D structure of the proteins were obtained using the input raw sequence obtained from the Uniprot

Swiss Model Database:

SWISS-MODEL is used to predict the closest matching 3D structure of the proteins using homology modeling techniques[6]. Tertiary or the 3D structures of the proteins were obtained using the input FASTA sequence.

Clustal Omega Database:

Evolutionary relationships can be seen via viewing Cladograms or Phylograms. Phylogenetic Tree construction of the same was done and evolutionary relations between the proteins were obtained[7]. With the Input FASTA sequence Multiple Sequence Alignment of the proteins of study were obtained from the Clustal Omega Database

String Database:

STRING is an online resource and biological database of known and anticipated protein–protein interactions. Experimental data, computer prediction methods, and publicly available text collections are all included in the STRING database.[8.] Protein-protein interactions are found in the STRING database.The edges represent the predicted functional associations.

Results

Primary Sequence Analysis-Protparam Database:

The linear sequence of amino acids constituted in the protein of study-SCN1A_HUMAN(Fig 1A), KCMA1_HUMAN (Fig 1B), CAC1A_HUMAN (Fig 1C) and AT1A2_HUMAN(Fig 1D) were obtained from Protparam Database.

The primary sequence analysis of SCN1A_HUMAN shows the following parameters- consists of 2009 aminoacids, molecular weight 228971.69, theoretical pI of 5.60. The instability index is 43.99 and the protein is classified unstable.

The primary sequence analysis of KCMA1_HUMAN shows the following parameters- consists of 1236 aminoacids, molecular weight 137559.53, theoretical pI of 6.66. The instability index is 53.01 and the protein is classified unstable.

The primary sequence analysis ofCAC1A_HUMAN shows the following parameters- consists of 2506 aminoacids, molecular weight of 282563.84, theoretical pI of 9.00. The instability index is 51.34 and the protein is classified unstable.

The primary sequence analysis of AT1A2_HUMAN shows the following parameters- consists of 1020 aminoacids, molecular weight 112265.64, theoretical pI of 5.47. The instability index is 33.33 and the protein is classified stable.

Fig 1A Linear sequence of protein SCN1A_HUMAN

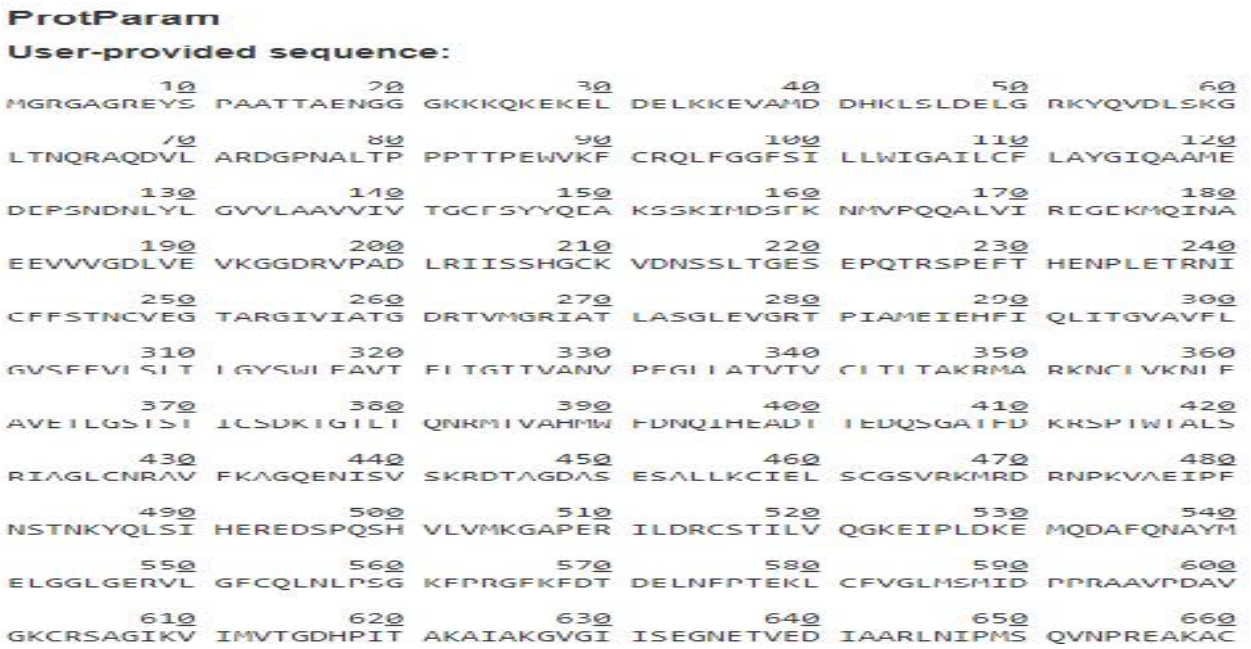


Fig 1B Linear sequence of protein KCMA1_HUMAN (Q12791)

ProtParam

User-provided sequence:

```
        10         20         30         40         50         60
MANGGGGGGG SSGGGGGGGG SSLRMSSNIH ANHLSLDASS SSSSSSSSSS SSSSSSSSSS

        70         80         90        100        110        120
VHEPKMDALI IPVTMEVPCD SRGQRMWWAF LASSMVTFFG GLFIILLWRT LKYLWTVCCH

       130        140        150        160        170        180
CGGKTKEAQK INNGSSQADG TLKPVDEKEE AVAAEVGWMT SVKDWAGVMI SAQTLTGRVL

       190        200        210        220        230        240
VVLVFALSIG ALVIYFIDSS NPIESCQNFY KDFTLQIDMA FNVFFLLYFG LRFIAANDKL

       250        260        270        280        290        300
WFWLEVNSVV DFFTVPPVFV SVYLNRSWLG LRFLRALRLI QFSEILQFLN ILKTSNSIKL

       310        320        330        340        350        360
VNLLSIFIST WLTAAGFIHL VENSGDPWEN FQNNQALTYW ECVYLLMVTM STVGYGDVYA

       370        380        390        400        410        420
KTTLGRLFMV FFILGGLAMF ASYVPEIIEL IGNRKKYGGS YSAVSGRKHI VVCGHITLES
```

Fig 1C Linear Sequence of CAC1A_HUMAN

ProtParam

User-provided sequence:

```
        10         20         30         40         50         60
MARFGDEMPA RYGGGGSGAA AGVVVGSGGG RGAGGSRQGG QPGAQRMYKQ SMAQRARTMA

        70         80         90        100        110        120
LYNPIPVRQN CLTVNRSLFL FSEDNVVRKY AKKITEWPPF EYMILATIIA NCIVLALEQH

       130        140        150        160        170        180
LPDDDKTPMS ERLDDTEPYF IGIFCFEAGI KIIALGFAFH KGSYLRNGWN VMDFVVVLTG

       190        200        210        220        230        240
ILATVGTEFD LRTLRAVRVL RPLKLVSGIP SLQVVLKSIM KAMIPLLQIG LLLFFAILIF

       250        260        270        280        290        300
AIIGLEFYMG KFHTTCFEEG TDDIQGESPA PCGTEEPART CPNGTKCQPY WEGPNNGITQ

       310        320        330        340        350        360
FDNILFAVLT VFQCITMEGW TDLLYNSNDA SGNTWNWLYF IPLIIIGSFF MLNLVLGVLS

       370        380        390        400        410        420
GEFAKERERV ENRRAFLKLR RQQQIERELN GYMEWISKAE EVILAEDETD GEQRHPFDAL
```

Fig 1D Linear sequence of protein AT1A2_HUMAN

ProtParam

User-provided sequence:

```
        10         20         30         40         50         60
MEQTVLVPPG PDSFNFFTRE SLAAIERRIA EEKAKNPKPD KKDDDENGPK PNSDLEAGKN

        70         80         90        100        110        120
LPFIYGDIPP EMVSEPLEDL DPYYINKKTF IVLNKGKAIF RFSATSALYI LTPFNPLRKI

       130        140        150        160        170        180
AIKILVHSLF SMLIMCTILT NCVFMTMSNP PDWTKNVEYT FTGIYTFESL IKIIARGFCL

       190        200        210        220        230        240
EDFTFLRDPW NWLDFTVITF AYVTEFVDLG NVSALRTFRV LRALKTISVI PGLKTIVGAL

       250        260        270        280        290        300
IQSVKKLSDV MILTVFCLSV FALIGLQLFM GNLRNKCIQW PPTNASLEEH SIEKNITVNY

       310        320        330        340        350        360
NGTLINETVF EFDWKSYIQD SRYHYFLEGF LDALLCGNSS DAGQCPEGYM CVKAGRNPNY

       370        380        390        400        410        420
GYTSFDTFSW AFLSLFRLMT QDFWENLYQL TLRAAGKTYM IFFVLVIFLG SFYLINLILA

       430        440        450        460        470        480
VVAMAYEEQN QATLEEAEQK EAEFQQMIEQ LKKQQEAAQQ AATATASEHS REPSAAGRLS

       490        500        510        520        530        540
DSSSEASKLS SKSAKERRNR RKKRKQKEQS GGEEKDEDEF QKSESEDSIR RKGFRFSIEG

       550        560        570        580        590        600
NRLTYEKRYS SPHQSLLSIR GSLFSPRRNS RTSLFSFRGR AKDVGSENDF ADDEHSTFED

       610        620        630        640        650        660
NESRRDSLFV PRRHGERRNS NLSQTSRSSR MLAVFPANGK MHSTVDCNGV VSLVGGPSVP
```

Secondary Sequence Analysis-SOPMA Database:

Prediction of secondary structure of protein-SCN1A_HUMAN (Fig 2A), KCMA1_HUMAN (Fig 2B), CAC1A_HUMAN (Fig 2C) and AT1A2_HUMAN (Fig 2D) were obtained from SOPMA Database. Alpha helix (α-helix) and beta-pleated sheet forms (β-*pleated sheet*) using the raw input sequence obtained from Uniprotkb .
The secondary sequence analysis of SCN1A_HUMAN (Fig 2A) shows the following parameters- alpha helix constitutes 46.04%, extended strand constitutes 14.98%, Beta turn constitutes 4.23%, Random coil constitutes 34.74%.

The secondary sequence analysis of KCMA1_HUMAN (Fig 2B) shows the following parameters- alpha helix constitutes 35.36%, extended strand constitutes 14.64%, Beta turn constitutes 4.53%, Random coil constitutes 45.47%.

The secondary sequence analysis ofCAC1A_HUMAN (Fig 2C) shows the following parameters- alpha helix constitutes 36.71%, extended strand constitutes 10.14%, Beta turn constitutes 4.39%, Random coil constitutes 48.76%.

The secondary sequence analysis of AT1A2_HUMAN(Fig 2D) shows the following parameters- alpha helix constitutes 39.90%, extended strand constitutes 21.47%, Beta turn constitutes 4.51%, Random coil constitutes 34.12%.

Fig 2A Secondary structure -SCN1A_HUMAN

Fig 2B Secondary structure- KCMA1_HUMAN

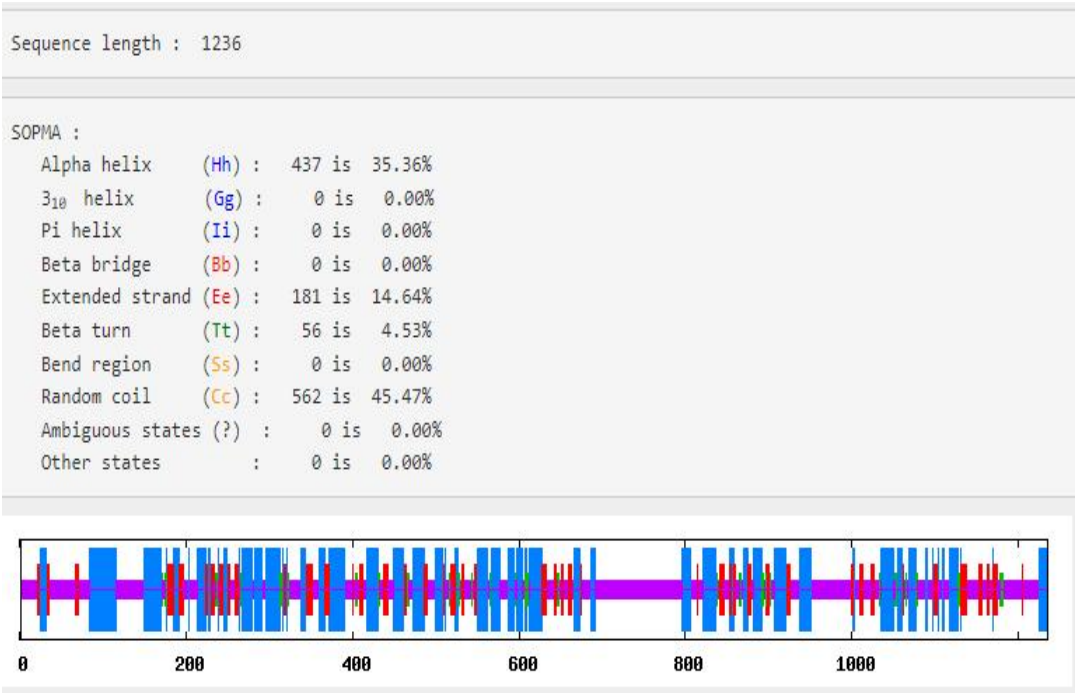


Fig 2C – Secondary Structure of CAC1A_HUMAN

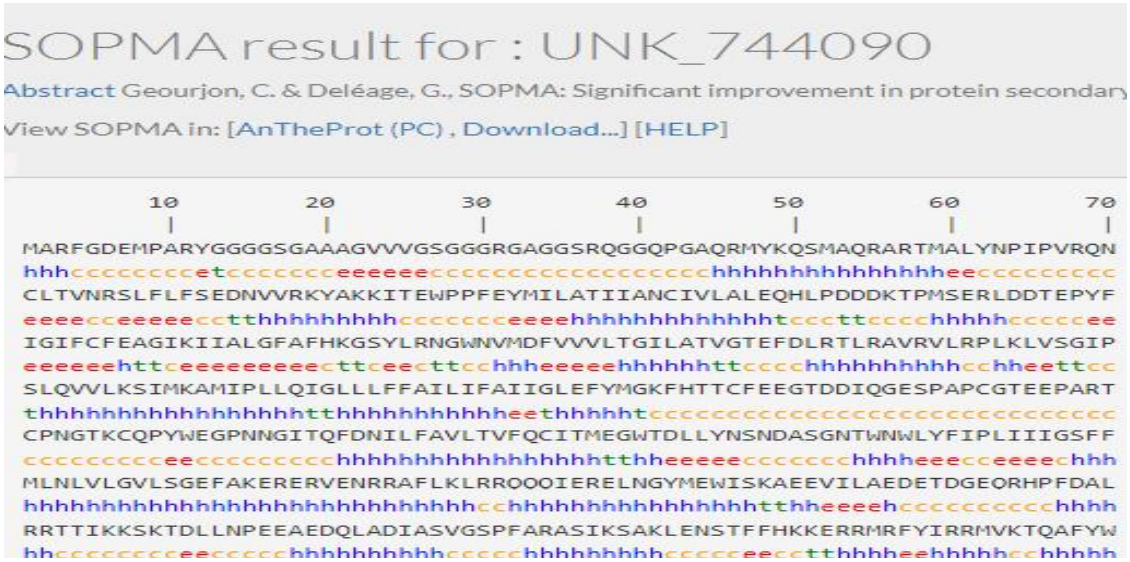
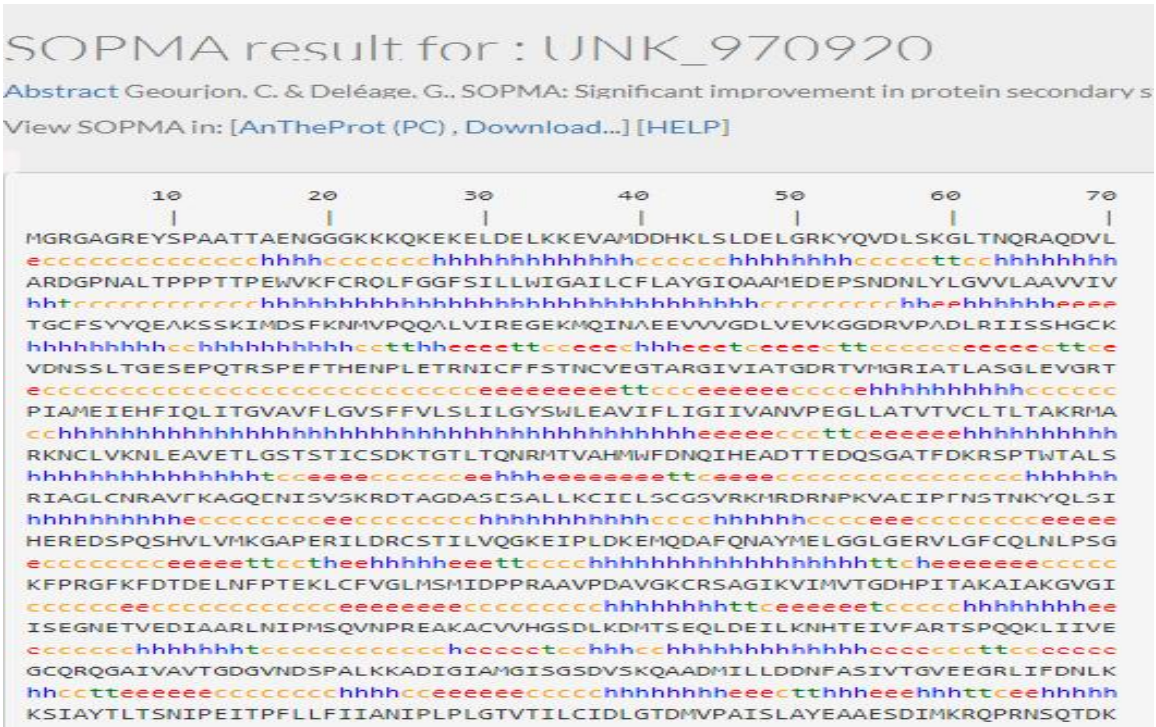


Fig 2D Secondary structure -AT1A2_HUMAN



Tertiary Structure Prediction

Prediction of 3D structure of proteins- - SCN1A_HUMAN(Fig 3A), KCMA1_HUMAN (Fig 3B), CAC1A_HUMAN (Fig 3C) and AT1A2_HUMAN(Fig 3D) were obtained from Alphafold database and Swissmodel database.

The tertiary structure of SCN1A_HUMAN is obtained from PDB database (PDB ID- 7DTD).
The tertiary structure of KCMA1_HUMAN is obtained from Alphafold Database.
The tertiary structure of CAC1A_HUMAN is obtained from PDB database (PDB ID- 3BXK)
The tertiary structure of AT1A2_HUMAN is obtained from Alphafold database.

Fig 3A Tertiary Structure of Protein SCN1A_HUMAN

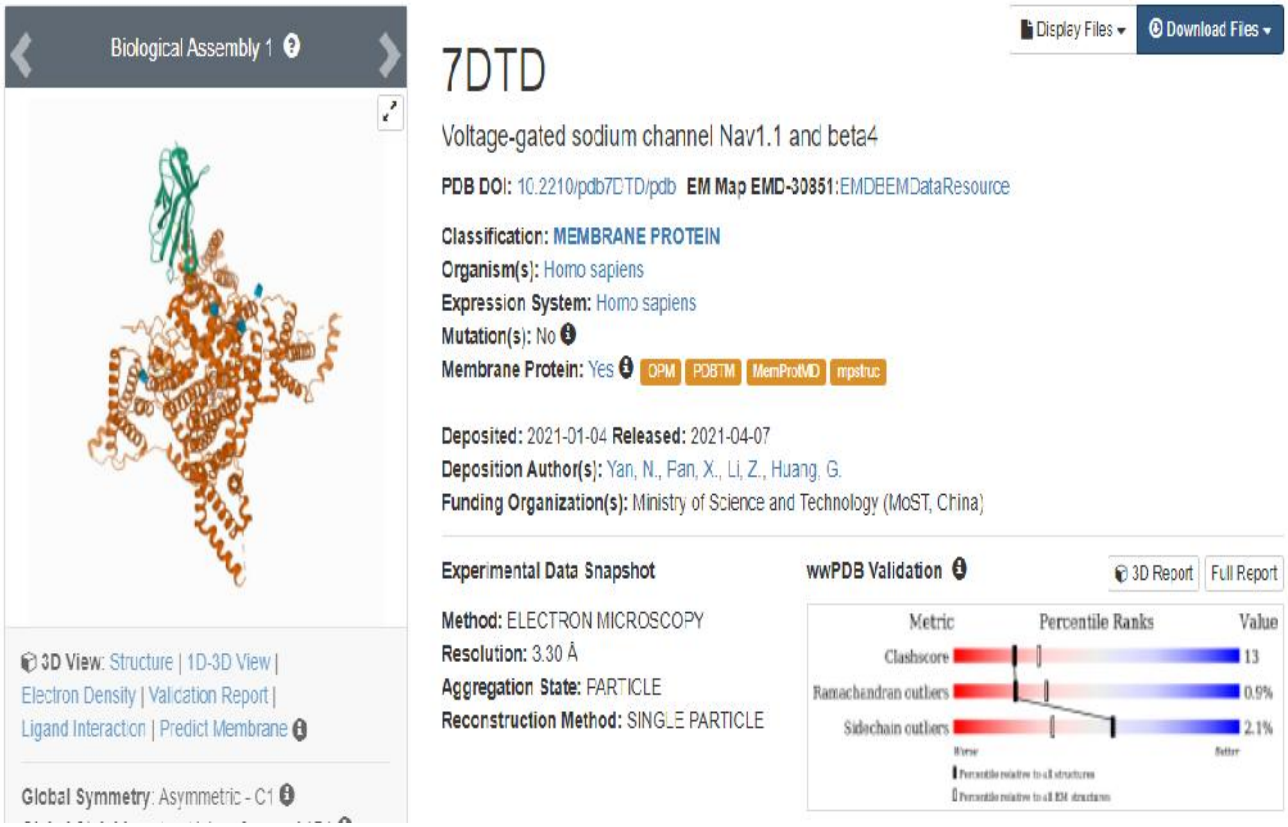


Fig 3B Tertiary Structure of KCMA1_HUMAN

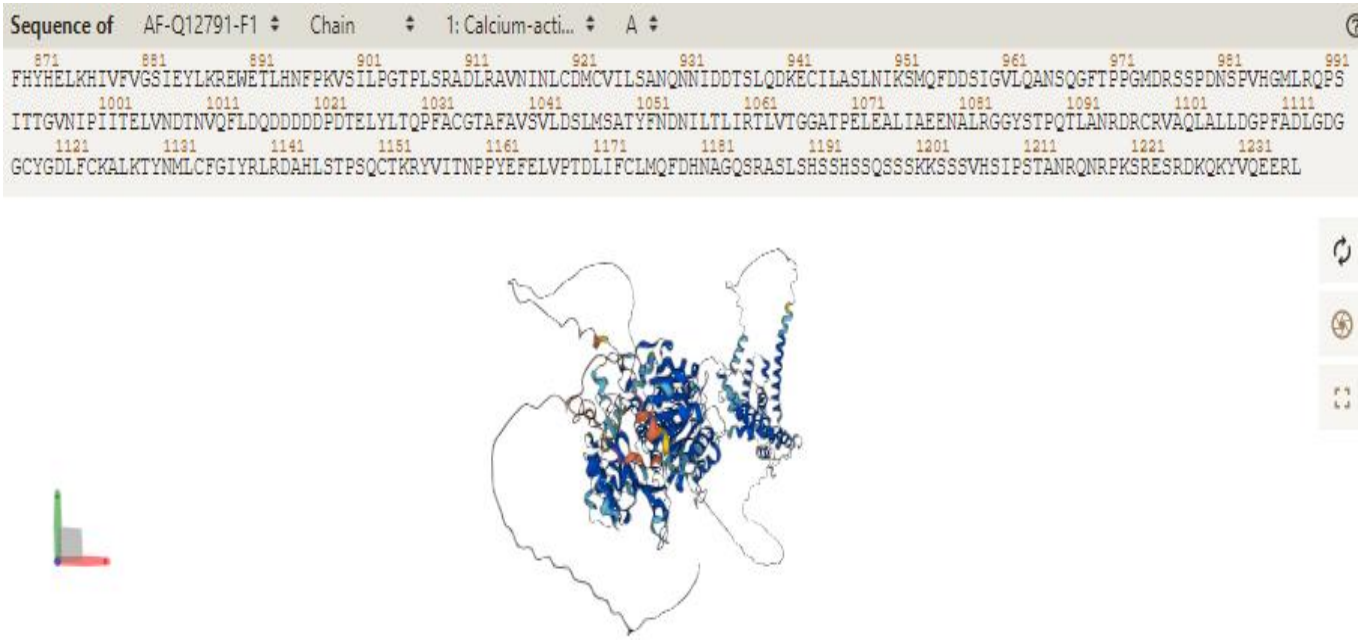


Fig 3C Tertiary Structure of CAC1A_HUMAN

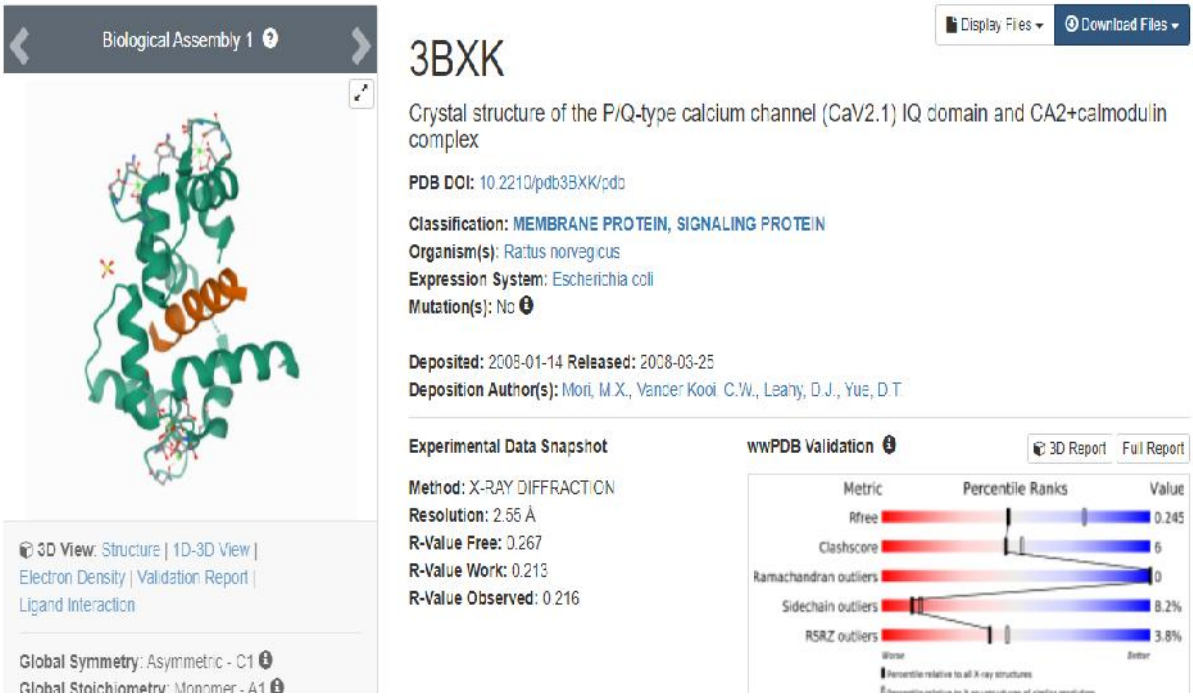


Fig 3D Tertiary Structure of AT1A2_HUMAN

Clustal Omega Database:

Multiple Sequence Alignment (Fig 4A) and Phylogenetic tree (Fig 4B, 4C) results are obtained for the 4 proteins, namely- Sodium channel protein type 1 subunit alphaUniprotKB ID - SCN1A_HUMAN(P35498) , Calcium-activated potassium channel subunit alpha-1-UniprotKB ID- KCMA1_HUMAN (Q12791)-associated with epilepsy ; Voltage-dependent P/Q-type calcium channel subunit alpha-1AUniprotKB ID- CAC1A_HUMAN(O00555), Sodium/potassium-transporting ATPase subunit alpha-2-UniprotKB ID-AT1A2_HUMAN(P50993) associated with migraine using Clustal Omega Database.

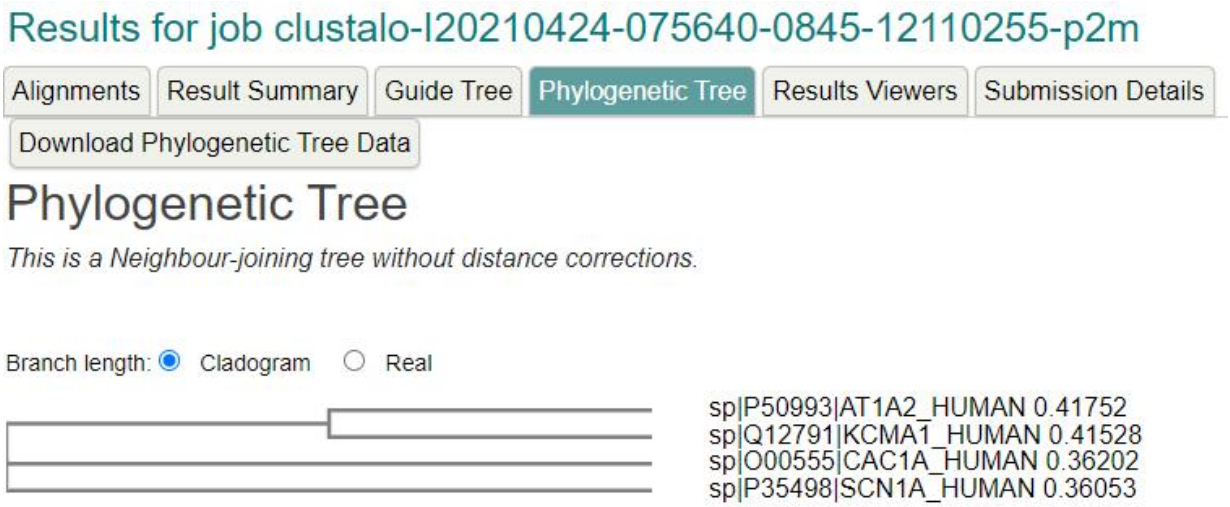
Phylogram(Fig 4B) result shows close association/common origin of proteins between Calcium-activated potassium channel subunit alpha-1-UniprotKB ID- KCMA1_HUMAN (Q12791), Voltage-dependent P/Q-type calcium channel subunit alpha-1AUniprotKB ID- CAC1A_HUMAN(O00555) and Sodium channel protein type 1 subunit alphaUniprotKB ID - SCN1A_HUMAN(P35498). Sodium/potassium-transporting ATPase subunit alpha-2-UniprotKB ID- AT1A2_HUMAN (P50993) has a different origin.

Phylogenetic Tree (Fig 4C) shows Sodium/potassium-transporting ATPase subunit alpha-2-UniprotKB ID- AT1A2_HUMAN (P50993) and Calcium-activated potassium channel subunit alpha-1-UniprotKB ID- KCMA1_HUMAN (Q12791) has a common node of origin. The Voltage-dependent P/Q-type calcium channel subunit alpha-1AUniprotKB ID- CAC1A_HUMAN(O00555) and Sodium channel protein type 1 subunit alpha UniprotKB ID - SCN1A_HUMAN(P35498) have a separate origin/evolution.

Fig 4A Multiple Sequence Alignment of the 4 proteins of study

Fig 4B phylogram

Fig 4C Phylogenetic tree construction



String Database:

String offers study of enhancement investigation. It particularly inquires for genome-scale input, with each protein or quality having related numerical esteem (an est imation or measurable metric).

TheFASTA sequence of SCN1A_HUMAN, KCMA1_HUMAN, CAC1A_HUMAN, AT1A2_HUMAN proteins were retrieved from UniProt and the best protein interaction is retrieved. The PPI Network of the above proteins consisted of 4 nodes, 5 edges, average node degree is 2.5, PPI enrichment p-value 3.64e-08. The figure shows interaction between the proteins taken into consideration. (Fig 5A, 5B,)

Fig 5A The PPI network using STRING software

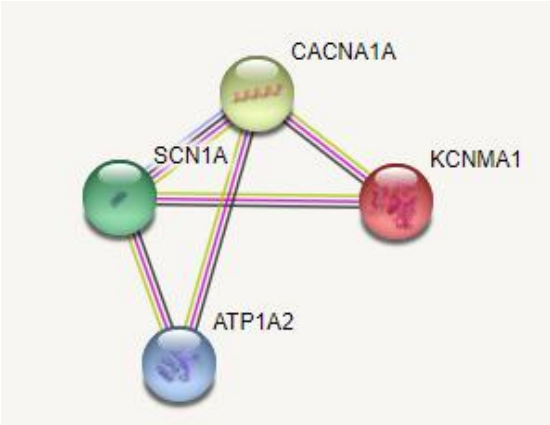


Fig 5B Biochemical activity relationship in STRING software

Discussion

Epilepsy and Migraine which are disorders of neuronal excitability wherein the ion channels play a critical in the regulation of the same. A large conductance of the $Ca2^{+}$-activated, K^{+} (BK_{Ca}) channel play an important role. The channels are activated by either membrane depolarization or increased intracellular Ca^{2+}. The unique coupling of Ca^{2+} signaling to membrane depolarization forms the basis in controlling neuronal hyper excitability, as an outward K^{+} current through BK_{Ca} channels hyperpolarizes neurons. Calcium, Potassium, Sodium channels Dysregulation and signaling are important factors that attribute to the pathogenesis of epilepsy and migraine. A significant approach towards development of targeted drug delivery on the diseased protein pump facilitates in the complete recovery of the patient without any drug induced adverse reactions systemically and further reduction in the repetition of episodes involved in the disease and significant improvement in the quality of life of the patient.

Conclusion

All the above evaluation concludes significant interaction and overlapping of proteins between epilepsy and migraine and subsequent interaction in molecular pathways and cell signalling. Futuristic approach towards signal pathway transduction studies and targeted drug delivery may pave an effective solution in the control of neuronal signaling of epilepsy and migraine.

Conflict of interest:

The authors declare they have no competing interests.

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