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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.<sup>1</sup>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(<u>P35498</u>) (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(000555) (migraine)

Sodium/potassium-transporting ATPase subunit alpha-2-UniprotKB ID-AT1A2\_HUMAN(<u>P50993</u>) (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.<sup>4</sup> 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.<sup>5</sup> 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<sup>6</sup>. 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<sup>7</sup>. 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.<sup>8</sup> 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,

Fig 1A Linear sequence of protein SCN1A\_HUMAN

ProtParam

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 of parameters- consists 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 of CAC1A\_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 analysis primary sequence of AT1A2\_HUMAN shows following the 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.

User-provid	ded sequence	e:			
1 <u>0</u>	2 <u>0</u>	3 <u>0</u>	4 <u>0</u>	50	6 <u>0</u>
MGRGAGREYS	PAATTAENGG	GKKKQKEKEL	DELKKEVAMD	DHKLSLDELG	RKYQVDLSKG
10	80	90	100	110	120
LTNQRAQDVL	ARDGPNALTP	PPTTPEWVKF	CRQLFGGFSI	LLWIGAILCF	LAYGIQAAME
130	110	150	160	170	180
DEPSNDNLYL	GVVLAAVVIV	TGCFSYYQEA	KSSKIMDSFK	NMVPQQALVI	REGEKMQINA
190	200	210	22 <u>0</u>	230	240
EEVVVGDLVE	VKGGDRVPAD	LRIISSHGCK	VDNSSLTGES	EPQTRSPEFT	HENPLETRNI
250	260	27 <u>0</u>	280	290	300
CFFSTNCVEG	TARGIVIATG	DRTVMGRIAT	LASGLEVGRT	PIAMEIEHFI	QLITGVAVEL
310	320	330	340	350	360
GVSEEVI SI T	I GYSUI FAVT	FITGTTVANV	PEGLIATVTV	CI TI TAKRMA	RKNCI VKNI F
370	380	39 <u>0</u>	400	410	420
AVEILGSISI	ICSDRIGILI	QNRMIVAHMW	FUNQIHEADI	TEDQSGATED	KRSPIWIALS
43 <u>0</u>	440	450	460	47 <u>0</u>	48 <u>0</u>
RIAGLCNRAV	FKAGQENISV	SKRDTAGDAS	ESALLKCIEL	SCGSVRKMRD	RNPKVAEIPF
49 <u>0</u>	500	510	52 <u>0</u>	530	54 <u>0</u>
NSTNKYQLSI	HEREDSPQSH	VLVMKGAPER	ILDRCSTILV	QGKEIPLDKE	MQDAFQNAYM
550	560	570	580	590	600
ELGGLGERVL	GFCQLNLPSG	KEPRGEKEDT	DELNFPTEKL	CFVGLMSMID	PPRAAVPDAV
610	620	630	640	650	660
GKCRSAGIKV	IMVTGDHPIT	AKAIAKGVGI	ISEGNETVED	IAARLNIPMS	QVNPREAKAC

#### Fig 1B Linear sequence of protein KCMA1\_HUMAN (Q12791)

#### ProtParam

#### User-provided sequence:

10 20 30 40 50 60 MANGGGGGGG SSGGGGGGG SSLRMSSNIH ANHLSLDASS SSSSSSSSS SSSSSSSSS 70 80 90 100 110 120 VHEPKMDALI IPVTMEVPCD SRGQRMWWAF LASSMVTFFG GLFIILLWRT LKYLWTVCCH CGGKTKEAQK INNGSSQADG TLKPVDEKEE AVAAEVGWMT SVKDWAGVMI SAQTLTGRVL VVLVFALSIG ALVIYFIDSS NPIESCONFY KDFTLQIDMA FNVFFLLYFG LRFIAANDKL 250 260 270 280 290 300 WFWLEVNSVV DFFTVPPVFV SVYLNRSWLG LRFLRALRLI QFSEILQFLN ILKTSNSIKL VNLLSIFIST WLTAAGFIHL VENSGDPWEN FQNNQALTYW ECVYLLMVTM STVGYGDVYA 37<u>0</u> 38<u>0</u> 39<u>0</u> 40<u>0</u> 41<u>0</u> 42<u>0</u> KTTLGRLFMV FFILGGLAMF ASYVPEIIEL IGNRKKYGGS YSAVSGRKHI VVCGHITLES 

#### Fig 1C Linear Sequence of CAC1A\_HUMAN

#### ProtParam

#### User-provided sequence:

MARFGDEMPA RYGGGGSGAA AGVVVGSGGG RGAGGSRQGG QPGAQRMYKQ SMAQRARTMA LYNPIPVRQN CLTVNRSLFL FSEDNVVRKY AKKITEWPPF EYMILATIIA NCIVLALEQH LPDDDKTPMS ERLDDTEPYF IGIFCFEAGI KIIALGFAFH KGSYLRNGWN VMDFVVVLTG ILATVGTEFD LRTLRAVRVL RPLKLVSGIP SLQVVLKSIM KAMIPLLQIG LLLFFAILIF AIIGLEFYMG KFHTTCFEEG TDDIQGESPA PCGTEEPART CPNGTKCQPY WEGPNNGITQ FDNILFAVLT VFQCITMEGW TDLLYNSNDA SGNTWNWLYF IPLIIIGSFF MLNLVLGVLS GEFAKERERV ENRRAFLKLR ROQQIERELN GYMEWISKAE EVILAEDETD GEORHPFDAL

Fig 1DLinear sequence of protein AT1A2\_HUMAN

#### ProtParam

```
User-provided sequence:
```

1 <u>0</u>	2 <u>0</u>	3 <u>0</u>	4 <u>0</u>	5 <u>0</u>	6 <u>0</u>
MEQTVLVPPG	PDSFNFFTRE	SLAAIERRIA	EEKAKNPKPD	KKDDDENGPK	PNSDLEAGKN
7 <u>0</u>	80	90	10 <u>0</u>	110	12 <u>0</u>
LPFIYGDIPP	EMVSEPLEDL	DPYYINKKTF	IVLNKGKAIF	RFSATSALYI	LTPFNPLRKI
13 <u>0</u>	140	150	160	17 <u>0</u>	18 <u>0</u>
AIKILVHSLF	SMLIMCTILT	NCVFMTMSNP	PDWTKNVEYT	FTGIYTFESL	IKIIARGFCL
190	200	210	22 <u>0</u>	23 <u>0</u>	24 <u>0</u>
EDFTFLRDPW	NWLDFTVITF	AYVTEFVDLG	NVSALRTFRV	LRALKTISVI	PGLKTIVGAL
25 <u>0</u>	26 <u>0</u>	27 <u>0</u>	28 <u>0</u>	29 <u>0</u>	30 <u>0</u>
IQSVKKLSDV	MILTVFCLSV	FALIGLQLFM	GNLRNKCIQW	PPTNASLEEH	SIEKNITVNY
31 <u>0</u>	320	33 <u>0</u>	34 <u>0</u>	35 <u>0</u>	36 <u>0</u>
NGTLINETVF	EFDWKSYIQD	SRYHYFLEGF	LDALLCGNSS	DAGQCPEGYM	CVKAGRNPNY
37 <u>0</u>	38 <u>0</u>	39 <u>0</u>	400	41 <u>0</u>	42 <u>0</u>
GYTSFDTFSW	AFLSLFRLMT	QDFWENLYQL	TLRAAGKTYM	IFFVLVIFLG	SFYLINLILA
43 <u>0</u>	440	45 <u>0</u>	46 <u>0</u>	47 <u>0</u>	48 <u>0</u>
VVAMAYEEQN	QATLEEAEQK	EAEFQQMIEQ	LKKQQEAAQQ	AATATASEHS	REPSAAGRLS
49 <u>0</u>	50 <u>0</u>	51 <u>0</u>	52 <u>Ø</u>	53 <u>0</u>	54 <u>0</u>
DSSSEASKLS	SKSAKERRNR	RKKRKQKEQS	GGEEKDEDEF	QKSESEDSIR	RKGFRFSIEG
55 <u>0</u>	56 <u>0</u>	57 <u>0</u>	58 <u>0</u>	59 <u>0</u>	600
NRLTYEKRYS	SPHQSLLSIR	GSLFSPRRNS	RTSLFSFRGR	AKDVGSENDF	ADDEHSTFED
61 <u>0</u>	62 <u>0</u>	63 <u>0</u>	64 <u>0</u>	650	66 <u>0</u>
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 ( -helix) and beta-pleated sheet forms ( -pleated sheet) using the raw input sequence obtained from Uniprotkb. secondary The 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 of CAC1A\_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

10	20	30	40	50	60	70
1	1	1	1	1	1	1
MEQTVLVPPGPDS	INFETRESLAA	IERRIAEEKA	KNPKPDKKDD	DENGPKPNSD	LEAGKNLPFI	YGDIPP
ecceeeccccccc	ceecchhhhhh	hhhhhhhhc	ecceccec	cecececee	hhttccccee	etcccc
EMVSEPLEDLDPYY	<b>VINKKTFIVLN</b>	KGKAIFRESA	TSALYILTPF	NPLRKIAIKI	LVHSLFSMLI	MCTILT
hhhccchhhccche	eccceeeee	ttceeeecc	cceeeeeccc	cchhhhhhhe	eehhhhhhhh	hhhht
NCVFMTMSNPPDWT	<b>KNVEYTFTGI</b>	YTFESLIKII	ARGFCLEDFT	FLRDPWNWLD	FTVITFAYVT	EFVDLG
cheeeeetcccccc	ccceeeeecco	<mark>cchhhhhhh</mark> h	httcccccee	eeccccchhh	eeeeehhhhh	hheett
NVSALRTFRVLRAU	KTISVIPGLK	TIVGALIQSV	KKLSDVMILT	VFCLSVFALI	GLQLFMGNLR	NKCIQW
cchhhhhhhhhhhh	hheeecttch	hhhhhhhhh	hhhhhheee	hhhhhhhhh	hhhhhhhcc	ccceec
PPTNASLEEHSIEH	(NITVNYNGTL	INETVFEFDW	KSYIQDSRYH	YFLEGFLDAL	LCGNSSDAGQ	CPEGYM
ccccccccchh	heeeccccee	eeecccccce	eeeectecce	eeecccchhe	eeccccccc	ccccee
CVKAGRNPNYGYTS	SFDTFSWAFLS	LFRLMTQDFW	ENLYQLTLRA	AGKTYMIFFV	LVIFLGSFYL	INLILA
eeettccttcceee	ecchhhhhhh	hhhhhhhhh	hhhhhhhhh	ttcceeeeee	eeeehhhhhh	hhhhhh
VVAMAYEEQNQATI	LEEAEQKEAEF	QUITEQUERQ	QEAAQQAATA	TASEHSREPS	AAGRESDSSS	EASKLS
nnnnnncchnn	hhnnnnnnnn	nnnnnnnnn	nnnnnnnnn	nnnncccccc	VERNAGEDUA	nhhhhn
SKSAKERRNRRKK	REQSOCE	KDEDEFQKSE	SEDSIRKKGF	RESIEGNELI	YEKRYSSPHQ	SLLSIR
	ESEDGDAKDW	SCENDEADDE			GERRNENLEO	TEDEED
USLF SPRRIVSRTST	LESEKORAKUW	SENDFADDE	hbbbbbbcccc	RUSEFVERR	GERRINSINESQ	ISKSSK
	EVECTOR NOVEL W	GDEVDTEDV	GOLL REVITE	VPATDDNGTT	TETEMPUPPS	CCEHVS
REAVERANCE			CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	COCCOCCOCC	chhhhhcccc	CCCEEE
	ISTASTI TNTV	FELEESBOKC	PPCWYKESNT	EL THIDOSPYH	I KVKHVVNI V	VMDPEV
hhhhccccchhhh	hhhhhhhhhhh	hhhhhhcccc	ccceeeebbb	eeeettooch	hhhhheeee	eectto
DLAITICIVLNTL	MAMEHYPMTD	HENNVLTVGN	LVFTGIFTAE	MELKIIAMDP	YYYFOEGWNI	FDGFIV
hhhhhhhhhhhhh	hhhtcccch	hhhhhettc	eeeeehhhhh	hhhhhecct	tceecttcch	hhhhee

#### Fig 2B Secondary structure- KCMA1\_HUMAN



### **Fig 2C** – Secondary Structure of CAC1A\_HUMAN

# SOPMA result for : UNK\_744090

Abstract Geourjon, C. & Deléage, G., SOPMA: Significant improvement in protein secondary View SOPMA in: [AnTheProt (PC) , Download...] [HELP]



## SOPMA result for : UNK\_970920

Abstract Geourion, C. & Deléage, G., SOPMA: Significant improvement in protein secondary s View SOPMA in: [AnTheProt (PC), Download...] [HELP]

10	20	30	40	50	60	70
1	1	1	1	1	1	1
MGRGAGREYSPAAT	TAENGGGKKK	QKEKELDELK	KEVAMDDHKL	SLDELGRKYQ	VDLSKGLTNQ	RAQDVL
eccccccccccc	chhhhccccc	cchhhhhhhh	hhhhhccccc	chhhhhhhhc	ccccttcchh	hhhhhh
ARDGPNALTPPPTT	PEWVKFCROL	FGGFSILLWI	GAILCFLAYG	IOAAMEDEPS	NDNLYLGVVL	AAVVIV
hhterecoreces	chhhhhhhhh	hhhhhhhhh	hhhhhhhhhh	hhbereer	cchheehhhh	hheeee
TGCFSYYQEAKSSK		QOALVIREGE	KMQINAEEVV	VGDLVEVKGG	DRVPADLRII	SSHGCK
hhhhhhhhcchh	hhhhhhhcct	thheeeetto	ceeechhhee	etceeectt	ccccccccccc	ecttce
VDNSSLTGESEPOT	RSPETTHENP	LETRNICFES	TNEVEGTARG	IVIATGDRTV	MGRIATLASG	LEVGRT
eccccccccccccc	cececece	ccccceeeee	eeeettccce	eeeeecccce	hhhhhhhhhh	eccecc
PTAMETEHETOL TT	GVAVEL GVSE	EVISITIONS	WI FAVTEL TO	TTVANVPEGI	LATVTVCLTL	TAKRMA
cchhhhhhhhhhhhhh	hhhhhhhhhh	hhhhhhhhh	hhhhhhhhh	eeeeccttc	eeeeebhhh	hhhhhh
RKNCI VKNI EAVET		KTGTI TONRM		THEADTTEDO	SGATEDKRSP	THTALS
hhhhhhhhhhhhhhh	htcceeeecc	cccceebbbe	eeeeeetto	eeeeccccc	concentre of	hhhhhh
BTAGL CNBAVEKAG		TAGDASESAL	LKCTEL SCGS	VEKMEDENEK	VALTPENSTN	KYOLST
hhhhhhhhhherco	conceence	ccccchhhhh	hhhhhhree	hhhhhcccc	eeeccoccc	CREARE
HEREDSPOSHVI VI	KGAPERTIDE			EONAYMEL GG	LGERVI GECO	INLESG
	ttootheehh	hhheettoo	cchhhhhhhhh	hhhhhhhhhh	ttchaeaeee	encer sa
KERRGEKEDTDELA	EDTEKI CEVG	IMSMTDPPPA	AVPDAVGKCP	SAGTKVTMVT	GDHRTTAKAT	AKGVGT
KIT KGI KI DIDEEL	WITTERECT VO	enonitorrika	ccchhhhhhh	bttreesee	torcobbbb	hhhhas
TEEGNETVEDTAAT	NT DIAS OVIND	DEAKACIANHG			TVEADTEDOO	KI TTVE
13EGRETVEDIAA	CENTENSONAE	REAKACUUNG	SUCKOPH SEQ		IVPARISPQQ	REIIVE
GCOROGATIVANTES	NEWDERALYK	ADTATAMATA	GEDVEROAAD		THTENEEGDI	TEDNIK
GCQRQGAIVAVIGL	JOVINDSPALKK	ADIGIANGIS	GSDVSKQAAD	MILLODNFAS	IVIGVEEGRE	IFDINER
KETAVTI TENTDET	TDELLETTAN		L CTDI GTDIO	DATELAYEAA	ECOTWKDODD	NEOTOK
KSTATILI SNIPEI	LIPPLLPIIAN	THEFTOIVIT	LCIDEGIDMV	PAISLAYEAA	ESDIMKRUPR	NSQIDK

### **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

Sequence of AF-Q12791-F1 \* Chain \* 1: Calcium-acti... \* A \*
O

571
581
591
901
921
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941
951
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1221
1231
<



#### Fig 3C Tertiary Structure of CAC1A\_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) , Calciumactivated potassium channel subunit alpha-1UniprotKB ID- KCMA1\_HUMAN (Q12791)associated with epilepsy ; Voltage-dependent P/Q-type calcium channel subunit alpha-1AUniprotKB ID- CAC1A\_HUMAN(000555), 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 KCMA1 HUMAN ID-(Q12791), Voltage-dependent P/Q-type calcium alpha-1AUniprotKB channel subunit ID-CAC1A\_HUMAN(000555) and Sodium channel protein type 1 subunit alphaUniprotKB ID -SCN1A\_HUMAN(P35498). Sodium/potassiumtransporting 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 and Calcium-activated potassium (P50993) 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(000555) and Sodium channel protein type 1 subunit alpha UniprotKB ID -SCN1A HUMAN(P35498) have a separate origin/evolution.

#### Fig 4AMultiple Sequence Alignment of the 4 proteins of study

Input form	Web services	Help & Docum	nentation Bio	informatics Tools I	=AQ	
Iools > Multip	ole Sequence Al	lignment > Clusta	al Omega			
Results	for iob clu	stalo-I2021	0425-2128	356-0507-:	31150	0995-p1m
Alignments	Result Summ	ary Guide Tree	Phylogenetic *	Free Results V	iewers	Submission Detai
Download A	Alignment File	Show Colors				
CLUSTAL 0(1.2.	4) multiple seque	nce alignment				
50 P50993 AT1A 50 Q12791 KCMA 50 P35498 SCN1 50 Q00555 CAC1	2 HUMAN 1 HUMAN A_HUMAN MEQT	VLVPPGPDSFNFFTRESL M	ANIERRIAEEKAKNPKPL A REGD EMD4	IKKDDDENGPKPNSDL	0 0 55 666 30	
	2 HUMAN				0	
500993 AT1A 50 Q12791 KCMA 50 P35498 SCN1 50 000555 CAC1	A_HUMAN A_HUMAN RGAG	EAGK NLPFIYGDIP	AQ RARIMALYNPTPVR	N CITY	NR5 //	

Fig 4B phylogram



sp|P50993|AT1A2\_HUMAN 0.449265 sp|Q12791|KCMA1\_HUMAN 0.4464 sp|O00555|CAC1A\_HUMAN 0.430562 sp|P35498|SCN1A\_HUMAN 0.430562

#### Fig 4C Phylogenetic tree construction

# Results for job clustalo-I20210424-075640-0845-12110255-p2m

Alignments Result Summary Guide Tree Phylogenetic Tree Results Viewers Submission Details

Download Phylogenetic Tree Data

# Phylogenetic Tree

This is a Neighbour-joining tree without distance corrections.

Branch length: 🖲	Cladogram	0	Real	

### **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). sp|P50993|AT1A2\_HUMAN 0.41752 sp|Q12791|KCMA1\_HUMAN 0.41528 sp|O00555|CAC1A\_HUMAN 0.36202 sp|P35498|SCN1A\_HUMAN 0.36053

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 5AThe 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<sup>+</sup>-activated,  $K^+(BK_{Ca})$  channel play an important role. The channels are activated by either membrane depolarization or increased intracellular Ca<sup>2+</sup>. The unique coupling of Ca<sup>2+</sup> signaling to membrane depolarization forms the basis in controlling neuronal hyper excitability, as an outward K<sup>+</sup> current through BK<sub>Ca</sub> channels hyperpolarizes neurons. Calcium, Potassium, Sodium channels Dysregulation and signaling are important factors that attribute to the pathogenesis of epilepsy and A significant approach towards migraine. 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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