Role of AnkyrinG in linking the spectrin-based membrane skeleton to integral membrane proteins the Na⁺/Ca⁺⁺ exchanger, the Na⁺/K⁺ ATPase, and voltage-gated sodium channels and its contribution to epilepsy

Sanjay Kumar Choubey[1], Prashant Srivastava[1], Saurabh Shukla[1] and Gomase V.S.[2]
[1]Yeshwant College of Information Technology (Bioinformatics & Biotechnology), Parbhani, MS
[2]School of Technology, S.R.T.M. University, Sub-Centre, Latur, 413512, India

Abstract- There are specific alterations in the structure or function of ion channels in the epileptic brain. Few of the alterations may trigger hyperexcitability and the others prevent nerve cells from being damaged due to epileptic discharges. Ion channels assist in regulation of the excitation in the CNS. Mutation in ion channel genes contributes to epileptic seizures. AnkyrinG, a family of adaptor proteins helps in association of integral membrane proteins to the spectrin-actin based membrane skeleton. Abscence of AnkyrinG expression may lead to impaired ability in generating action potential. Sodium ion channel requires AnkyrinG for its proper localization. In absence of AnkyrinG clustering of voltage gated sodium channel is affected which is required for generating action potential.

INTRODUCTION

Ankyrin are a family of adaptor proteins that helps in the association of integral membrane proteins to the spectrin based skeleton. Ankyrin have binding sites for the beta subunit of spectrin and for about 12 families of integral membrane proteins.This association is needed to maintain the integrity of plasma mem,brane to stem many ion channels and ion transporters in the palsmamembrane.Ankyrins are encoded by thre genes ANK1, ANK2 and ANK3. The products of ANK1, ANK2 and ANK3 are ankyrinR, ankyrinB and ankyrinG proteins respectively.Out of the above three proteins encoded by ankyrin genes, ankyrinB and ankyrinG have been recognized in neurons.AnkyrinB and AnkyrinG proteins are required for chaged distribution of several membrane proteins like Na+/K+ ATPase and voltage gated sodium channel. AnkyrinG has been found involved in the biopolar disorder.Ankyrin brings about intracellular trafficking of alpha1-Na+-K+-ATPase in polarized cells. Alteration in ankyrin contributed to many hereditary disorders which is due to improper localization of membrane proteins. Ankyrin dependent pathway for transport of Na+-k+ -ATPase is facilitated by assembly of ion channels in presence of Ankyrin.Ankyrin consists of 3 major domains: a membrane binding domain with a like folding structure and 24 cosecutive repetts called MB domain, a spectrin-binding domain and a death domain called DC domain. Interaction with ankyrinG is vital for the localization of voltage gated sodioum channels to at the axon initial and for neurons to trigger action potentials. The conserved 9-aminoacid motif is required for ankyrinG binding and to channelize sodium ion channel to various excitable membrane domain. This motif has been also confirmed in ion channel proteins KCNQ2 and KCNQ3.

METHODOLOGY

The amino acid sequence for AnkyrinG is retrieved from SWISS-PROT database. The retrieved amino acid was subjected for domain prediction. Interproscan tool was used for domain prediction. All the three different domains were displayed by Interproscan. We downloaded PDB file of ankyrin to predict the active site .1UOH file was downloaded in PDB format. Active site of Ankyrin was predicted using Active site prediction server software. We retrived the amino acid sequence for KCNQ2 and KCNQ3 Nav from SWISS-PROT database. Using Activesite prediction tool we predicted the cavities of Ankyrin which will bind to ligand molecule. We predicted domian of KCNQ2 and KCNQ3 using nine amino acids transactivation domain prediction tool.

RESULT AND DISCUSSION

We studied the cavities of Ankyrin protein which binds to Sodium and Potassium ion channel proteins to localize ion-channels in proper direction so as to trigger action potential.

Cavities	
cavity_1_NQCVKYASHWDGLPTR	cavity_2_YISQVDNAEGTKPLH
cavity_3_ENDYHLGARQKCSW	cavity_4_DKANHPVCTGYQELM
cavity_5_QGEANMLVPKDRITFH	cavity_6_VQNCKAHWDGSPTLR
cavity_7_WAKSDLPRIGVCYETH	cavity_8_TQSKLAVERYGHIN
cavity_9_KPLYNTAGVHIEQMDR	cavity_10_YETILSQVRNMAGPDKH
cavity_11_KEQGTNDIYHPLARCS	cavity_12_GMASLDKRYEIVTHF
cavity_13_VNCTKAGHQLDMPSREI	cavity_14_ALYWGKESVMHNPRIDT
cavity_15_DTQIEYKSHANGRPVLC	cavity_16_SNAIVGTMQPDKLEYH
cavity_17_EKGQNVDTAIYPLR	cavity_18_VPALKGTSQEFID
cavity_19_QDNIESKTHPLYAGRVC	cavity_20_NDPSTVHKLARGCQFEI
cavity_21_KGALSNYVHERIMD	cavity_22_KELVARGHN
cavity_23_ISKTDANLHPVYGQEM	cavity_24_RNCLATSVYMDIFGKE
cavity_25_DKSNQPTHVLRGCA	cavity_26_SWRYVCGAHTNIMKLE
cavity_27_YLGEVKRISMAQH	cavity_28_AVLTEQFHISGK
cavity_29_EQKYTLINGVAD	cavity_30_DRQWSTNLVCYAMHK
cavity_31_EQKYTNILSVGA	cavity_32_EYTNKISQGDP
cavity_33_LGAIKEVR	

Fig1: Activeste Cavities for Ankyrin Protein

Sanjay Kumar Choubey, Prashant Srivastava, Saurabh Shukla and Gomase VS

**Nine Amino Acids Transactivation Domain
(9aa TAD) Prediction Tool**

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ANALYSED SEQUENCE:

```
MVQKSRNGGVYPGPSGEKKLKVGFVGLDPGAPDSTRDGALLIAGSEAPKRGSILSKPRAGGAGAGKPPKR 70
NAFYRKLQNFLYNVLERPRGWAFIYHAYVFLLVFSCLVLSVFSTIKEYEKSSEGALYILEIVTIVVFGVE 140
YFVRIWAAGCCCRYRGWRGRLKFARKPFCVIDIMVLIASIAVLAAGSQGNVFATSALRSLRFLQILRMIR 210
MDRRGGTWKLLGSVVYAHSKELVTAWYIGFLCLILASFLVYLAEKGENDHFDTYADALWWGLITLTTIGY 280
GDKYPQTWNGRLLAATFTLIGVSFFALPAGILGSGFALKVQEQHRQKHFEKRRNPAA GLIQSAWRF YATN 350
LSRTDLHSTWQYYERTVTVPMYSSQTQTYGASRLIPPLNQLELLRNLKSKSGLAFRKDPPPEPSPSKGSP 420
CRGPLCGCCPGRSSQKVSLKDRVFSSPRGVAAKGKGSPQAQTVRRSPSADQSLEDSPSKVPKSWSFGDRS 490
RARQAFRIKGAASRQNSEEASLPGEDIVDDKSCPCEFVTEDLTPGLKVSIRAVCVMRFLVSKRKFKESLR 560
P YDVMDVIEQ YSAGHLDMLSRIKSLQSRVDQIVGRGPAITDKDRTKGPAEAELPEDPSMMGRLGKVEKQV 630
LSMEKKLDFLVNIYMQRMGIPPTETEAYFGAKEPEPAPPYHSPEDSREHVDRHGCIVKIVRSSSSTGQKN 700
FSAPPAAPPVQCPPSTSWQPQSHPRQGHGTSPVGDHGSLVRIPPPPAHERSLSAYGGGNRASMEFLRQED 770
TPGCRPPEGNLRDSDTSISIPSVDHEELERSFSGFSISQSKENLDALNSCYAAVAPCAKVRPYIAEGESD 840
TDSDLCTPCGPPPRSATGEGPFGDVGWAGPRK 872
```

PERFECT MATCH   POOR MATCH

The results of the 9aaTAD jury:

Sequence	Start	End	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	
NAFYRKLQN	71	79	+	-	-	-	-	+	+	-	-	-	+	+	wrong match - NAFYRKLQN
QNFLYNVLE	78	86	+	+	+	+	+	+	+	+	-	+	+	+	wrong match - QNFLYNVLE
NFLYNVLER	79	87	+	+	+	+	+	+	+	+	-	+	+	+	wrong match - NFLYNVLER
EYFVRIWAA	140	148	+	+	-	+	+	-	+	+	+	+	+	+	wrong match - EYFVRIWAA
MVLIASIAV	174	182	+	+	+	-	-	-	+	+	+	+	+	+	wrong match - MVLIASIAV
GLIQSAWRF	338	346	+	+	+	+	+	+	+	+	+	+	+	+	
YDVMDVIEQ	562	570	+	+	+	+	+	+	+	+	+	+	+	+	

perfect match - GLIQSAWRF

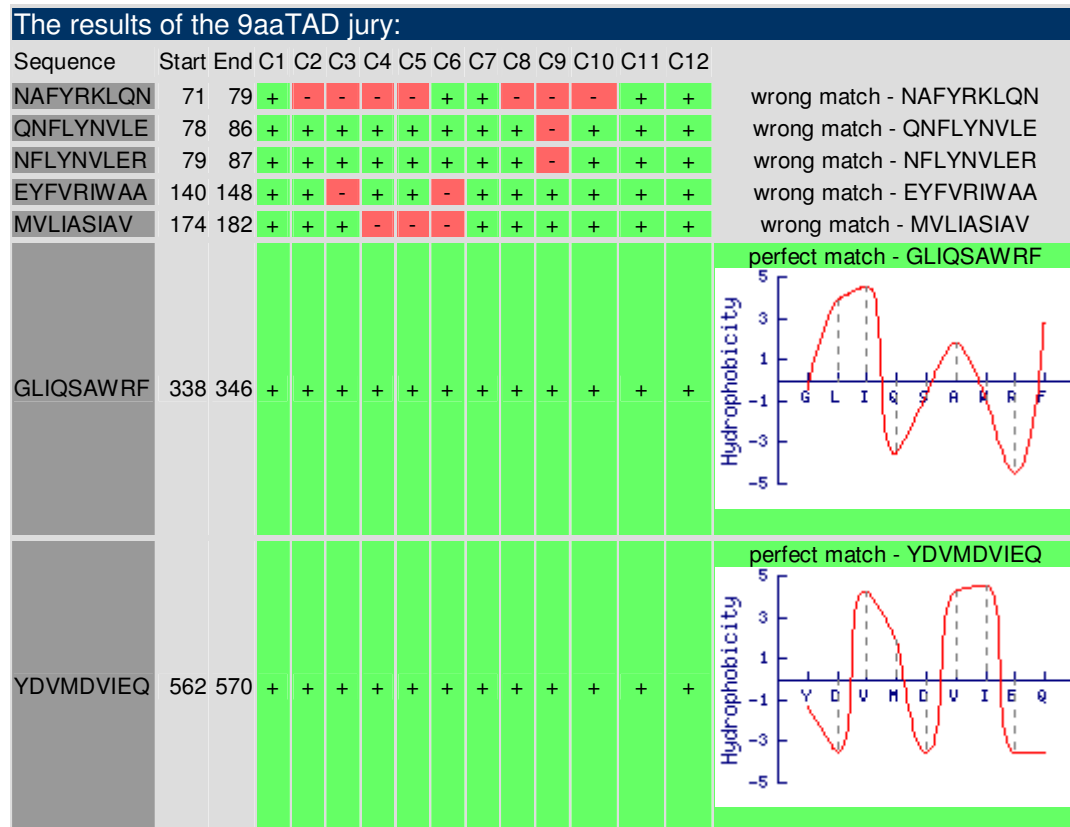perfect match - YDVMDVIEQ

Fig: 2   Domain prediction of HUMAN_ KCNQ2

**Nine Amino Acids Transactivation Domain
(9aa TAD) Prediction Tool**

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ANALYSED SEQUENCE:

MGLKARRAAGAAGGGGDGGGGGGGGAANPAGGDAAAAGDEERKVGLAPGDVEQVTLALGAGADKDGTLLLE 70
GGGRDEGQRRTPQGIGLLAKTPLSRPVKRNNAKYRRIQ TLIYDALER PRGWALLYHALVFLIVLGCLILA 140
VLTTFKEYETVSGDWLLLLETFAIFIFGAEFALRIWAAGCCCRYKGWRGRLKFARKPLCMLDIFVLIASV 210
PVVAVGNQGNVLATSLRSLRFLQILRMLRMDRRGGTWKLLGSAICAHSKELITAWYI GFLTLILSS LV Y 280
LVEKDVPEVDAQGEEMKEEFETYADALWWGLITLATIGYGDKTPKTWEGRLIAATFSLIGVSFFALPAGI 350
LGSGLALKVQEQHRQKHFEKRRKPAA ELIQAAWRY YATNPNRIDLVATWRFYESVVSFPFFRKEQLEAAS 420
SQKLGLLDRVRLSNPRGSNTKGKLFTPLNVDAIEESPSKEPKPVGLNNKERFRTAFRMKAYAFWQSSEDA 490
GTGDPMAEDRGYGNDFPIEDMIPTLKAAIRAVRILQFRLYKKKFKETLRPYDVKDVIEQYSAGHLDMLSR 560
IKYLQTRIDMIFTPGPPSTPKHKKSQKGSAFTFPSQQSPRNEPYVARPSTSEIEDQSMMGKFVKVERQVQ 630
DMGKKLDFLVDMHMQHMERLQVQVTEYYPTKGTSSPAEAEKKEDNRYSDLKTIICNYSETGPPEPPYSFH 700
QVTIDKVSPYGFFAHDPVNLPRGGPSSGKVQATPPSSATTYVERPTVLPILTLLDSRVSCHSQADLQGPY 770
SDRISPRQRRSITRDSDTPLSLMSVNHEELERSPSGFSISQDRDDYVFGPNGGSSWMREKRYLAEGETDT 840
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PERFECT MATCH   POOR MATCH

The results of the 9aaTAD jury:

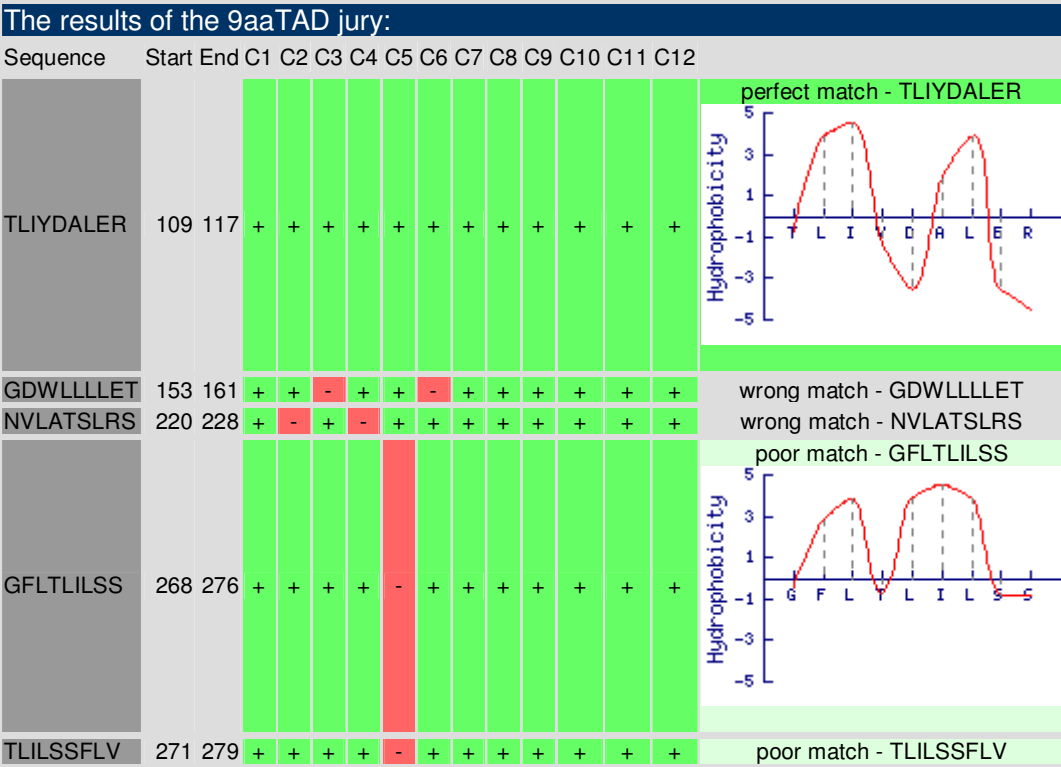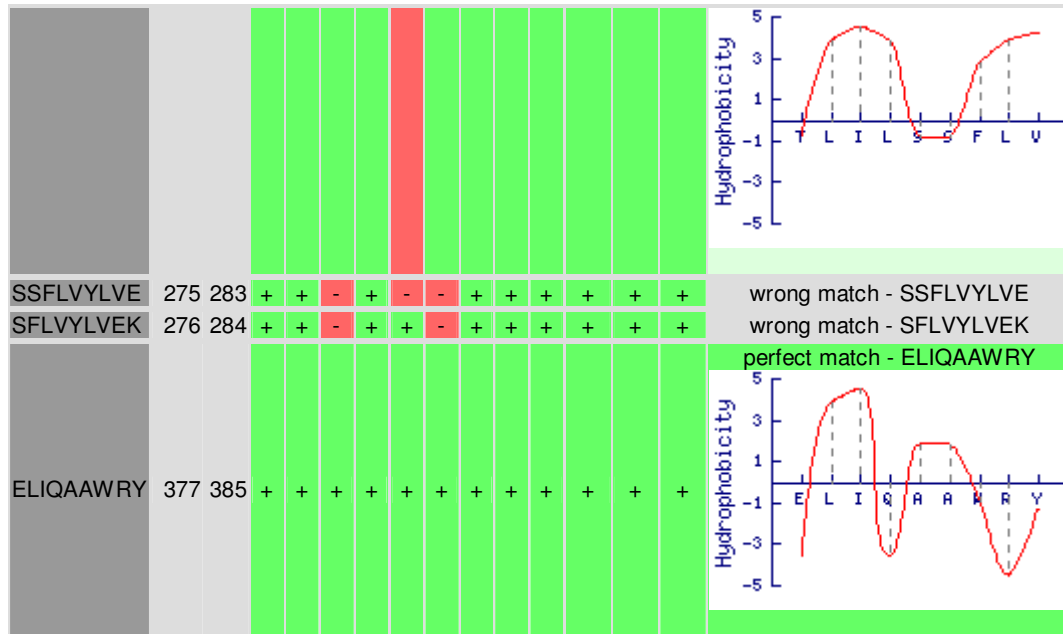| Sequence	Start	End	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	
TLIYDALER	109	117	+	+	+	+	+	+	+	+	+	+	+	+	perfect match - TLIYDALER
GDWLLLLET	153	161	+	+	-	+	+	-	+	+	+	+	+	+	wrong match - GDWLLLLET
NVLATSLRS	220	228	+	-	+	-	+	+	+	+	+	+	+	+	wrong match - NVLATSLRS
GFLTLILSS	268	276	+	+	+	+	-	+	+	+	+	+	+	+	poor match - GFLTLILSS
TLILSSFLV	271	279	+	+	+	+	-	+	+	+	+	+	+	+	poor match - TLILSSFLV

Fig: 3 Domain prediction of HUMAN_KCNQ3

Nine Amino Acids Transactivation Domain (9aa TAD) Prediction Tool

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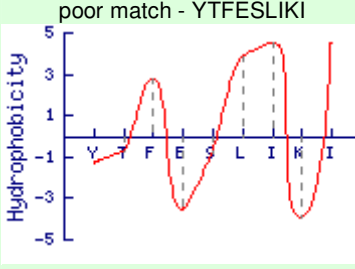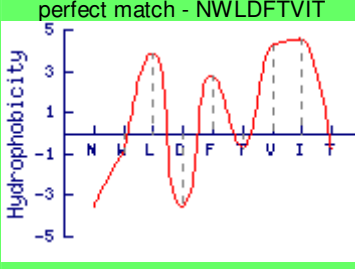now kindly hosted by the Spanish EMBnet Node

ANALYSED SEQUENCE:
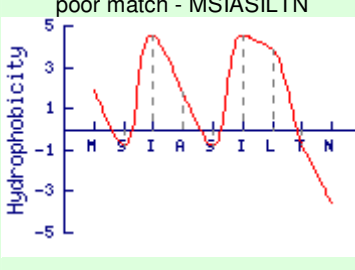
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NCVFMTMSNPPDWTKNVEYTFTGI YTFESLIK IARGFCLEDFTFLRDPW NWLDFTVIT FAYVTEFVDLG 210
NVSALRTFRVLRALKTISVIPGLKTIVGALIQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCIQW 280
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VVAMAYEEQNQATLEEAEQKEAEFQQMIEQLKKQQEAAQQAATATASEHSREPSAAGRLSDSSSEASKLS 490
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GSLFSPRRNSRTSLFSFRGRAKDVGSENDFADDEHSTFEDNESRRDSLFVPRRHGERRNSNLSQTSRSSR 630
MLAVFPANGKMHSTVDCNGVVSLVGGPSVPTSPVGQLLPEVIIDKPATDDNGTTTETEMRKRRSSSFHVS 700
MDFLEDPSQRQRA MSIASILTN TVEELEESRQKCPPCWYKFSNIFLIWDCSPYWLKVKHVVNLVVMDPFV 770
DLAITICIVLNTLFMAMEHYPMTDHFNNVLTVGNLVFT GIFTAEMFL KIIAMDPYYYFQEGWNIFDGFIV 840
TLSLVELGLANVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVGALGNLTLVLAIIVFIFAVVGMQ 910
LFGKSYKDCVCKIASDCQLPRWHMNDFFHSFLIVFRVLC GEWIETMWD CMEVAGQAMCLTVFMMVMVIGN 980
LVVLNLFLALLLSSFSADNLAATDDDNEMNNLQIAVDRMHKGVAYVKRKIYEFIQQSFIRKQKILDEIKP 1050
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QFMEFEKLSQFAAALEPPLNLPQPNKLQLIAMDLPMVSGDRIHCLDILFAFTKRVLGESGEMDALRIQME 1890
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IDRINENSITEKTDLTMSTAACPPSYDRVTKPIVEKHEQEGKDEKAKGK 2009

PERFECT MATCH   POOR MATCH

The results of the 9aaTAD jury:

Sequence	Start	End	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	
YTFESLIKI	165	173	-	+	+	+	+	+	+	+	+	+	+	+	poor match - YTFESLIKI
ESLIKIIAR	168	176	+	+	-	+	+	+	+	-	+	+	+	+	wrong match - ESLIKIIAR
NWLDFTVIT	191	199	+	+	+	+	+	+	+	+	+	+	+	+	perfect match - NWLDFTVIT
GALIQSVKK	238	246	+	-	+	+	+	-	+	-	+	-	+	+	wrong match - GALIQSVKK
TLINETVFE	303	311	+	+	+	-	+	+	-	+	+	+	+	+	wrong match - TLINETVFE
TVFEFDWKS	308	316	+	-	+	-	+	+	+	+	+	+	+	+	wrong match - TVFEFDWKS
DTFSWAFLS	366	374	+	+	+	+	-	-	+	+	+	+	+	+	wrong match - DTFSWAFLS
QDFWENLYQ	381	389	+	+	+	-	-	+	+	+	-	+	+	+	wrong match - QDFWENLYQ
TYMIFFVLV	398	406	+	+	-	-	-	-	+	+	+	+	+	+	wrong match - TYMIFFVLV
YMIFFVLVI	399	407	+	+	-	-	-	-	+	+	+	+	+	+	wrong match - YMIFFVLVI
MIFFVLVIF	400	408	+	+	-	-	-	-	+	+	+	+	+	+	wrong match - MIFFVLVIF
YLINLILAV	413	421	+	+	+	-	-	-	+	+	+	+	+	+	wrong match - YLINLILAV
NLILAVVAM	416	424	+	+	-	-	-	-	+	+	+	+	+	+	wrong match - NLILAVVAM
QQMIEQLKK	445	453	+	-	+	-	-	+	+	-	-	-	+	+	wrong match - QQMIEQLKK
MSIASILTN	714	722	+	+	+	+	-	+	+	+	+	+	+	+	poor match - MSIASILTN

Sequence	Start	End	1	2	3	4	5	6	7	8	9	10	11	12	Match
SILTNTVEE	718	726	+	-	+	-	+	+	-	+	+	+	+	+	wrong match - SILTNTVEE
NTLFMAMEH	781	789	+	+	-	+	+	-	+	+	+	+	+	+	wrong match - NTLFMAMEH
GIFTAEMFL	809	817	+	+	+	+	-	+	+	+	+	+	+	+	poor match - GIFTAEMFL
EMFLKIIAM	814	822	+	+	-	+	+	-	+	+	+	+	+	+	wrong match - EMFLKIIAM
GNLTLVLAI	891	899	+	+	+	+	-	-	+	+	+	+	+	+	wrong match - GNLTLVLAI
TLVLAIIVF	894	902	+	+	-	-	-	-	+	+	+	+	+	+	wrong match - TLVLAIIVF
NDFFHSFLI	935	943	+	+	+	+	+	+	+	+	-	+	+	+	wrong match - NDFFHSFLI
GEWIETMWD	950	958	+	+	+	+	+	+	+	+	+	+	+	+	perfect match - GEWIETMWD
TVFMMVMVI	970	978	+	+	-	-	-	-	+	+	+	+	+	+	wrong match - TVFMMVMVI
NLVVLNLFL	980	988	+	+	+	+	+	-	+	+	-	+	+	+	wrong match - NLVVLNLFL
NLFLALLLS	985	993	+	+	-	+	-	-	+	+	+	+	+	+	wrong match - NLFLALLLS
NNLQIAVDR	1010	1018	+	+	+	-	-	+	+	+	-	+	+	+	wrong match - NNLQIAVDR
EFIQQSFIR	1032	1040	+	+	+	-	+	+	-	+	-	+	+	+	wrong match - EFIQQSFIR
SSVEKYIID	1090	1098	-	+	+	-	+	+	+	+	+	+	+	+	poor match - SSVEKYIID
NWFETFIVF	1218	1226	+	+	+	+	+	-	+	+	+	+	+	+	wrong match - NWFETFIVF
ETFIVFMIL	1221	1229	+	+	-	+	-	-	+	+	+	+	+	+	wrong match - ETFIVFMIL
TFIVFMILL	1222	1230	+	+	-	-	-	-	+	+	+	+	+	+	wrong match - TFIVFMILL
YIFILEMLL	1261	1269	+	+	+	-	-	-	+	+	+	+	+	+	wrong match - YIFILEMLL
EMLLKWVAY	1266	1274	+	+	-	+	+	-	+	+	+	+	+	+	wrong match - EMLLKWVAY
DFLIVDVSL	1288	1296	+	-	+	+	+	-	+	+	+	+	+	+	wrong match - DFLIVDVSL
DIMYAAVDS	1436	1444	+	+	-	+	+	-	+	+	+	+	+	+	wrong match - DIMYAAVDS
ESLYMYLYF	1455	1463	+	+	-	+	-	-	+	+	+	+	+	+	wrong match - ESLYMYLYF
MYLYFVIFI	1459	1467	+	+	-	-	-	-	+	+	+	+	+	+	wrong match - MYLYFVIFI
SFFTLNLFI	1471	1479	+	+	+	+	-	+	+	+	+	+	+	+	poor match - SFFTLNLFI

GVIIDNFNQ	1480	1488	+	-	+	+	+	-	+	+	+	-	+	+	wrong match - GVIIDNFNQ
GMVFDFVTR	1532	1540	+	+	+	+	+	-	+	+	+	+	+	+	wrong match - GMVFDFVTR
DFVTRQVFD	1536	1544	+	+	+	-	+	+	+	+	-	+	+	+	wrong match - DFVTRQVFD

perfect match - QVFDISIMI

QVFDISIMI	1541	1549	+	+	+	+	+	+	+	+	+	+	+	+	

perfect match - NMVTMMVET

NMVTMMVET	1554	1562	+	+	+	+	+	+	+	+	+	+	+	+	

poor match - EYVTTILSR

EYVTTILSR	1567	1575	+	+	+	-	+	+	+	+	+	+	+	+	

TTILSRINL	1570	1578	+	-	+	-	+	+	+	+	+	+	+	+	wrong match - TTILSRINL
NLVFIVLFT	1577	1585	+	+	-	+	-	-	+	+	+	+	+	+	wrong match - NLVFIVLFT
NIFDFVVVI	1605	1613	+	+	+	+	+	-	+	+	+	+	+	+	wrong match - NIFDFVVVI
DFVVVILSI	1608	1616	+	+	-	+	-	-	+	+	+	+	+	+	wrong match - DFVVVILSI
GMFLAELIE	1618	1626	+	+	+	+	+	-	+	+	+	+	+	+	wrong match - GMFLAELIE
MFLAELIEK	1619	1627	+	+	+	+	+	-	+	+	+	+	+	+	wrong match - MFLAELIEK

perfect match - ELIEKYFVS

ELIEKYFVS	1623	1631	+	+	+	+	+	+	+	+	+	+	+	+	

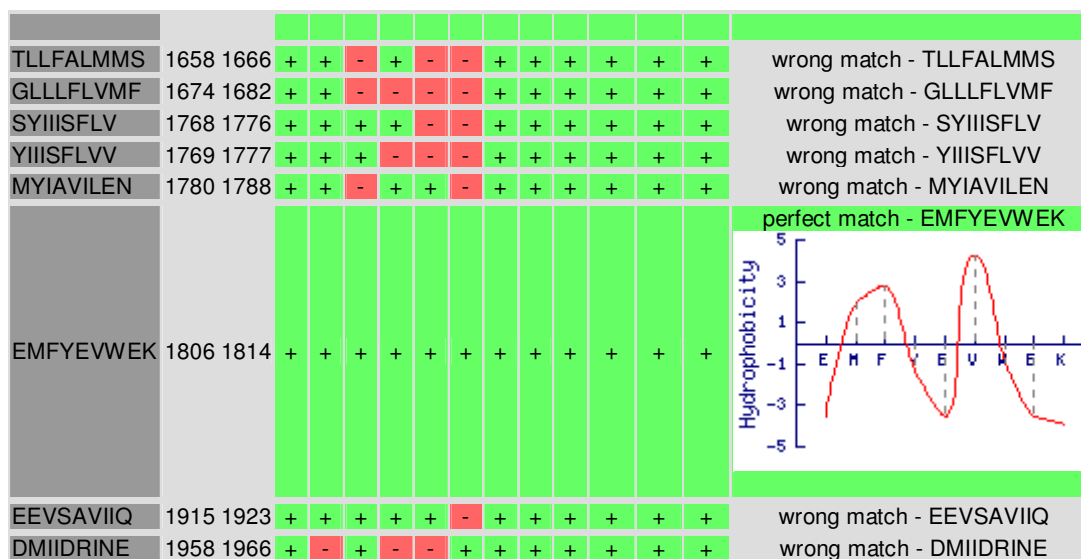| Peptide	Start	End													Match
TLLFALMMS	1658	1666	+	+	-	+	-	-	+	+	+	+	+	+	wrong match - TLLFALMMS
GLLLFLVMF	1674	1682	+	+	-	-	-	-	+	+	+	+	+	+	wrong match - GLLLFLVMF
SYIIISFLV	1768	1776	+	+	+	+	-	-	+	+	+	+	+	+	wrong match - SYIIISFLV
YIIISFLVV	1769	1777	+	+	+	-	-	-	+	+	+	+	+	+	wrong match - YIIISFLVV
MYIAVILEN	1780	1788	+	+	-	+	+	-	+	+	+	+	+	+	wrong match - MYIAVILEN
EMFYEVWEK	1806	1814	+	+	+	+	+	+	+	+	+	+	+	+	perfect match - EMFYEVWEK
EEVSAVIIQ	1915	1923	+	+	+	+	+	-	+	+	+	+	+	+	wrong match - EEVSAVIIQ
DMIIDRINE	1958	1966	+	-	+	-	-	+	+	+	+	+	+	+	wrong match - DMIIDRINE

Fig4: Domain prediction of HUMAN_SCN1A

CONCLUSION

Ankyrin plays a very important role in association of ion channels –both sodium and potassium ion channel which is essential in generating action potential. If there is any alteration in AnkyrinG it is going to affect the movement of ions across ion channels and may be a leading cause of impairment in functioning of Central nervous system.

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