Computational Analysis of Voltage-gated Potassium Channels

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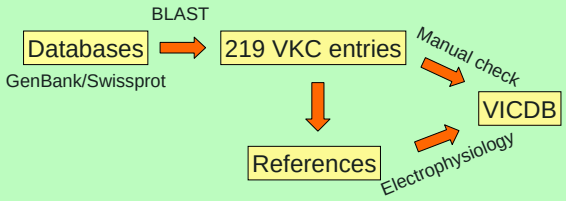
http://401hub.biology.ualberta.ca/~hzhang/VICDB

Introduction

We are developing a set of computational tools for the general problem of extracting information on the structure-function relationship within a family of proteins from comparative analyses of the sequences and functional characteristics of protein family members. Our effort is focused on the voltage-gated potassium channel (VKC) family. VKCs are a family of intrinsic membrane proteins that sense a change in the transmembrane electric field and open a pore for the passage of potassium ions across the lipid bilayer. VKCs perform regulatory functions in all excitable cell types. Defective VKCs can cause severe diseases, such as cardiac arrhythmia and epilepsy. Studies on VKCs may thus lead to better understanding of the pathogenesis of these VKC-related diseases.

Method

Data Collection



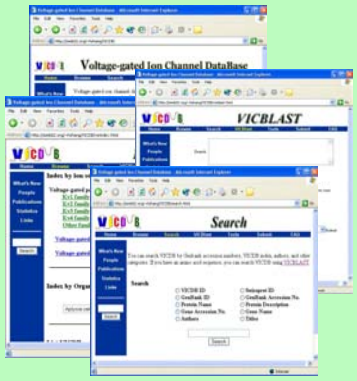
Data Processing

PepTool Multiple Alignment and manual adjustment. Only stably aligned sequence blocks were kept.

Data Analysis

Computation of pooled variance of $V_{1/2}$ at each position from individual variances of $V_{1/2}$ for identical residues.

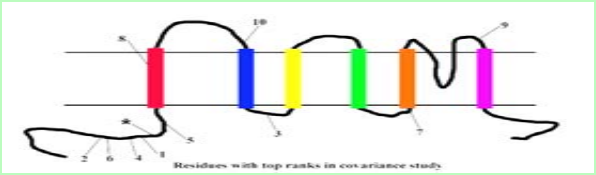
VICDB: Voltage-gated Ion Channel DataBase



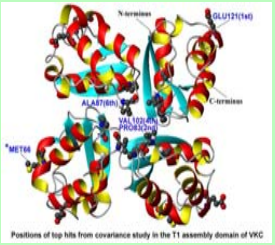
VICDB was built to serve as a resource for studies in voltage-gated ion channels. Perl scripts were used to direct over 200 BLAST searches and obtain over 300 VKC entries from GenBank/Swissprot. The sequences, references and other functional annotations were extracted into VICDB, a MySQL relational database. All entries were then manually checked for redundancy, sequence conflicts, isoforms and reference annotations. Currently, VICDB contains 219 nonredundant VKCs, and all entries are hyperlinked to their possible variant entries, entries with sequence conflicts, and 20 biological databases. We also searched through over 200 journal articles, and collected all the available VKC electrophysiological and pharmacological data into VICDB. VICDB can be browsed and searched by various categories. A local BLAST service is also implemented to allow users to compare query sequence with VICDB entries.

Results of covariance study

The top-ranked positions (lowest pooled variance) were most likely involved in determining the $V_{1/2}$ values of VKC.

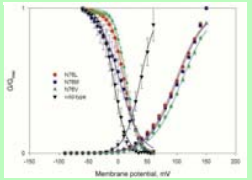


Structure of tetrameric T1 domain of VKC



Mapped to the T1 domain of VKC, the top hits from covariance study appear to locate at either the complementary interface or the outside of the T1 complex, indicating their possible roles in T1 assembly or interaction with other regions of VKC.

Experimental confirmation



Three mutants of the *P. penicillatus* jShak1 channel (N76 = *M66, above) shift the voltage-dependence of activation. Val102 mutations were also shown to affect $V_{1/2}$ by another group (Cell 102:657-670).

Summary and future directions

1.VICDB stores 219 VKCs with their structural, electrophysiological and other functional data.
2.Covariance analysis and mutagenesis data both indicate that a significant component of the variation of voltage sensitivity may depend on the structure of the T1 cytoplasmic domain.
3.Machine learning approaches are also being evaluated in structural-functional studies of VKC.

Acknowledgement

This research was supported by a grant from CIHR.

ISMB 2002