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TMFunction: database for functional residues in membrane proteins

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ABSTRACT

We have developed the database TMFunction, which is a collection of more than 2900 experimentally observed functional residues in membrane proteins. Each entry includes the numerical values for the parameters IC50 (measure of the effectiveness of a compound in inhibiting biological function), V_{max} (maximal velocity of transport), relative activity of mutants with respect to wild-type protein, binding affinity, dissociation constant, etc., which are important for understanding the sequence–structure–function relationship of membrane proteins. In addition, we have provided information about name and source of the protein, Uniprot and Protein Data Bank codes, mutational and literature information. Furthermore, TMFunction is linked to related databases and other resources. We have set up a web interface with different search and display options so that users have the ability to get the data in several ways. TMFunction is freely available at http://tmbeta-genome.cbrc.jp/TMFunction/.

INTRODUCTION

Membrane proteins perform a diverse variety of functions and are used as main drug targets of pharmaceutical agents. The collection of information on potential amino acid residues for the function of membrane proteins is important for understanding the sequence–structure–function relationship of membrane proteins as well as predicting the functional residues from sequence/structure. Tusnady *et al*. (1) constructed a database for transmembrane proteins, which covers the three-dimensional structures of membrane proteins deposited in Protein Data Bank (PDB) and information on membrane spanning α-helices and β-strands obtained with the TMDET algorithm (2). Saier *et al*. (3) developed a comprehensive classification system for membrane transport proteins known as the Transport Classification Database (TCDB). Further, functional databases have been developed for G-protein-coupled receptors (GPGRs), human seven transmembrane receptors, *Arabidopsis* integral membrane proteins and so on (4,5). Edvardsen *et al*. (6) created a G-protein-coupled receptor mutant database, which is mainly focused on different families of GPCRs. Mutational databases have also been developed for the structure, function and thermodynamics of proteins (7,8). On the other hand, several methods have been proposed for discriminating transmembrane α-helical and β-strand proteins, predicting their membrane-spanning segments, and functional classification of membrane proteins (9–16). In spite of these studies, there is no database available for the broad collection of potential residues, which are important for the functions of different classes of membrane proteins including receptors, transporters, channel proteins, etc. This information can be obtained from experimental studies on membrane proteins that have reported the measured values of several parameters for membrane protein function. The collection of such data is important and necessary for analyzing and predicting potentially important residues for practical applications.

In this work, we have developed a database, TMFunction, which is a collection of more than 2900 experimental data about important amino acid residues in membrane proteins, reported in the literature. It has information about functionally important residues, numerical values for the parameters IC50, V_{max}, activity, affinity, etc., along with sequence and structure information for the protein, mutational and literature information. This database will help in understanding the relationship between amino acid sequences/structures and functions of membrane proteins. We have developed a WWW interface to facilitate searching the database and displaying the results with different options.

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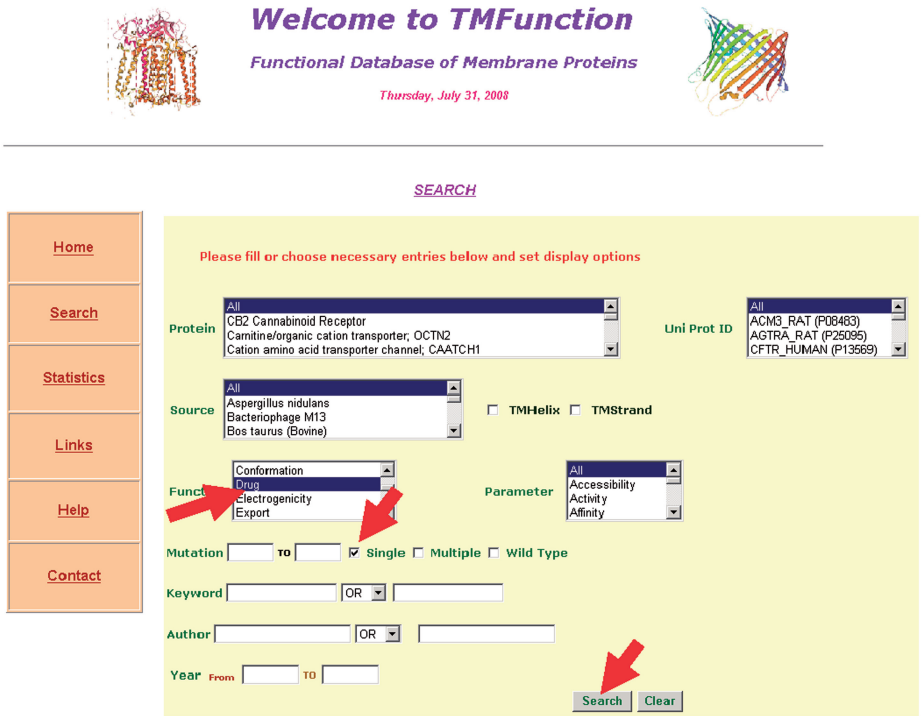
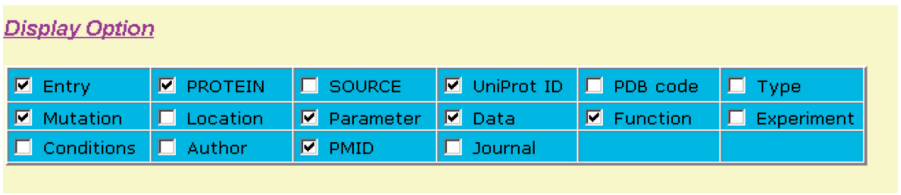
(**a**)



(**b**)



(**c**)

Search Results

Search Conditions

Function	Drug
Mutation	Single
Parameter	All
Protein	All
Source	All
UniProt ID	All

HIT: 198

No.	Protein	UniProt ID	Mutation	Parameter	Data	Function	PubMed ID
187	Multidrug resistance protein 1; MRP1	MRP1_HUMAN (P33527)	S1233A	Relative resistance factor to vincristine	12.5	Drug resistance	11925441
188	Multidrug resistance protein 1; MRP1	MRP1_HUMAN (P33527)	S1235A	Relative resistance factor to vincristine	9.3	Drug resistance	11925441
189	Multidrug resistance protein 1; MRP1	MRP1_HUMAN (P33527)	Y1236F	Relative resistance factor to vincristine	4.8	Drug resistance(partial)	11925441
190	Multidrug resistance protein 1; MRP1	MRP1_HUMAN (P33527)	S1237A	Relative resistance factor to vincristine	13.7	Drug resistance	11925441
191	Multidrug resistance protein 1; MRP1	MRP1_HUMAN (P33527)	Q1239A	Relative resistance factor to vincristine	17.3	Drug resistance	11925441
192	Multidrug resistance protein 1; MRP1	MRP1_HUMAN (P33527)	T1241A	Relative resistance factor to vincristine	4.4	Drug resistance	11925441
193	Multidrug resistance protein 1; MRP1	MRP1_HUMAN (P33527)	Y1243F	Relative resistance factor to vincristine	4.2	Drug resistance(partial)	11925441
194	Multidrug resistance protein 1; MRP1	MRP1_HUMAN (P33527)	N1245A	Relative resistance factor to vincristine	29.3	Drug resistance(partial)	11925441
198	Multidrug resistance protein 1; MRP1	MRP1_HUMAN (P33527)	S1233A	Relative resistance factor to VP-16	13.3	Drug resistance	11925441

Figure 1. An example of searching conditions, display options and results of TMFunction: (**a**) main menu for the search options in TMFunction. The items function (drug) and single mutants are selected for search as indicated by arrows; (**b**) display options in TMFunction. We have selected entry, protein, Uniprot ID, mutation, parameter, data, function and PMID to show in the output; (**c**) part of the results obtained from TMFunction.

CONTENTS OF THE DATABASE

Each entry in the database includes the following information:

Sequence and structure information: name and source of the protein, Uniprot (17) and PDB (18) codes, type of the integral membrane protein (α-helical or β-strand), mutational details (single, double or wild-type; mutation has been identified with mutated residue, residue number and mutant residue; e.g. A102V) and location of mutants.

Functional information: factors that are mainly affected by the mutation of amino acid residues in membrane proteins, such as relative activity of mutants, affinity for binding, channel, drug, glycosylation, membrane insertion, cellular signaling, membrane translocation, transport, etc.

Functional data: numerical values for affinity (%), B_{max}, IC50, drug sensitivity, K_d, K_m, V_{max}, uptake (%), etc.

Experimental methods and conditions: measurement, method and the ligand used for the control data.

Literature information: keywords, reference, authors and remarks.

DATABASE STATISTICS

The first release of TMFunction contains 2907 entries from 83 different proteins, which perform 29 diverse functions. It has data for 2092 single mutants, 580 multiple mutants and 273 wild-types. The majority of the data concerns transmembrane helical proteins (2760) followed by β-barrel membrane proteins (147). The data are obtained from more than 100 scientific articles published in 20 different journals.

FEATURES OF TMFUNCTION

TMFunction includes several features in the search and display options as shown in Figure 1, and as briefly explained subsequently:

(i) Retrieving data for a particular protein and/or source.
(ii) Specifying the type of the mutant as single, multiple and/or wild-type.
(iii) Selecting the function of the protein (transport) as well as the numerical value of the functional parameter (e.g. IC50).
(iv) Mentioning the type of the protein.
(v) Extracting data by authors, publication year and keywords.
(vi) Downloading entire data.

Detailed tutorials describing the usage of TMFunction are available at the home page. For example, the data obtained for the function 'drug' and single mutants is shown in Figure 1a. The terms: entry, protein, Uniprot ID, mutation, parameter, data, function, experiments and Pubmed ID have been selected for displaying the results (Figure 1b). Figure 1c shows the final results obtained with the search conditions and display options.

LINKS TO OTHER DATABASES

Each entry in TMFunction is linked to Uniprot ID (http://www.uniprot.org/) and PDB code (http://www.rcsb.org) to obtain the sequence and structure information directly. The references for all data are directly connected to the PUBMED literature database of NCBI (http://www.ncbi.nlm.nih.gov/pubmed/). Further, we have provided links to several related databases and web servers including sequences and structures, functions and genomes, transmembrane helix and strand predictions (http://tmbeta-genome.cbrc.jp/TMFunction/DBlinkspage.html).

AVAILABILITY AND CITATION OF TMFUNCTION

The database can be freely accessible at http://tmbeta-genome.cbrc.jp/TMFunction/. If this database is used as a tool in your published research work, please cite this article including the URL. Suggestions and comments are welcome and should be sent to michael-gromiha@aist.go.jp.

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