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Database

Volume 8(20)

DB Dehydrogenase: an online integrated structural database on enzyme dehydrogenase

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Received September 26, 2012; Accepted October 04, 2012; Published October 13, 2012

Abstract:
Dehydrogenase enzymes are almost inevitable for metabolic processes. Shortage or malfunctioning of dehydrogenases often leads to several acute diseases like cancers, retinal diseases, diabetes mellitus, Alzheimer, hepatitis B & C etc. With advancement in modern-day research, huge amount of sequential, structural and functional data are generated everyday and widens the gap between structural attributes and its functional understanding. DB Dehydrogenase is an effort to relate the functionalities of dehydrogenase with its structures. It is a completely web-based structural database, covering almost all dehydrogenases [~150 enzyme classes, ~1200 entries from ~160 organisms] whose structures are known. It is created by extracting and integrating various online resources to provide the true and reliable data and implemented by MySQL relational database through user friendly web interfaces using CGI Perl. Flexible search options are there for data extraction and exploration. To summarize, sequence, structure, function of all dehydrogenases in one place along with the necessary option of cross-referencing; this database will be utile for researchers to carry out further work in this field.

Availability: http://www.bifku.in/DBD/

Keywords: Dehydrogenase, Database, Oxidoreductase, Structure, Annotation

Background:
Dehydrogenases (DHs) or oxidoreductases are a group of well studied enzymes that catalyze transfer of protons from substrate to an acceptor or coenzymes, such as NAD or NADP or FAD or FMN in an oxidation-reduction reaction **[1].** DHs are generally characterized by two domains, one substrate binding domain and another co-enzyme binding domain. The coenzyme binding domain illustrates Rossman folds **[2]** for binding the dinucleotide or mononucleotide coenzyme and is practically the most conserved part of the protein. On the other hand, due to the immense diversity in the range of substrates catalysed by DHs, from steroids, prostaglandins, sugars, dyes, porphyrins, acids to alcohols, the substrate-binding pocket demonstrate high variability. As a matter of fact, DHs are classic examples of proteins where two domains (co-enzyme binding and substrate binding) of the same proteins are considered as separate evolutionary units.

DHs are essential in most of the metabolic pathways, both aerobic and anaerobic, including Glycolysis, TCA cycle, oxidative phosphorylation and amino acid metabolism in living cells. DHs as well take part in several pathways of various type of cancers i.e. breast cancer **[3],** prostrate cancer **[4]** and diverse life style disorders. DHs also serve as novel drug targets viz. glucose-6-phosphate dehydrogenase of trypanosomatids**, [5]** 11β-hydroxy steroid dehydrogenase 1 for cardiovascular and

other metabolic diseases, **[6]** type 1 inosine monophosphate dehydrogenase as an anti-angiogenic drug target [**7**]. On the other hand, lactate dehydrogenase acts as a biomarker for hemolysis-associated NO resistance, endothelial dysfunction and end-organ vasculopathy **[8].** Aldehyde dehydrogenase 1β1 does the same for human colon cancer **[9]** and glutamate dehydrogenase for acute hepatic injury **[10].**

In this situation, existence of vast number of members makes the classification very cloudy, our effort is to explore and reclassify the enzyme dehydrogenase on the basis of their available sequential, structural and functional data and put them all at one place to make it more comprehensive. We here, built a completely web based structural database on dehydrogenase, based on published structures from almost 160 species. This database contains brief pathway, co-enzyme, co-factor information, disease association, sequences, taxonomic characteristics, structural details, references and links to other resources of all entries.

Methodology of development

The relational database was developed, using MySQL as back end. The website is powered by Apache HTTP Server, HTML, JavaScript and CGI-PERL based web interfaces have been developed to execute the SQL queries dynamically. The application layer between the web interface and the backend relational tables has been implemented by using CGI-PERL.

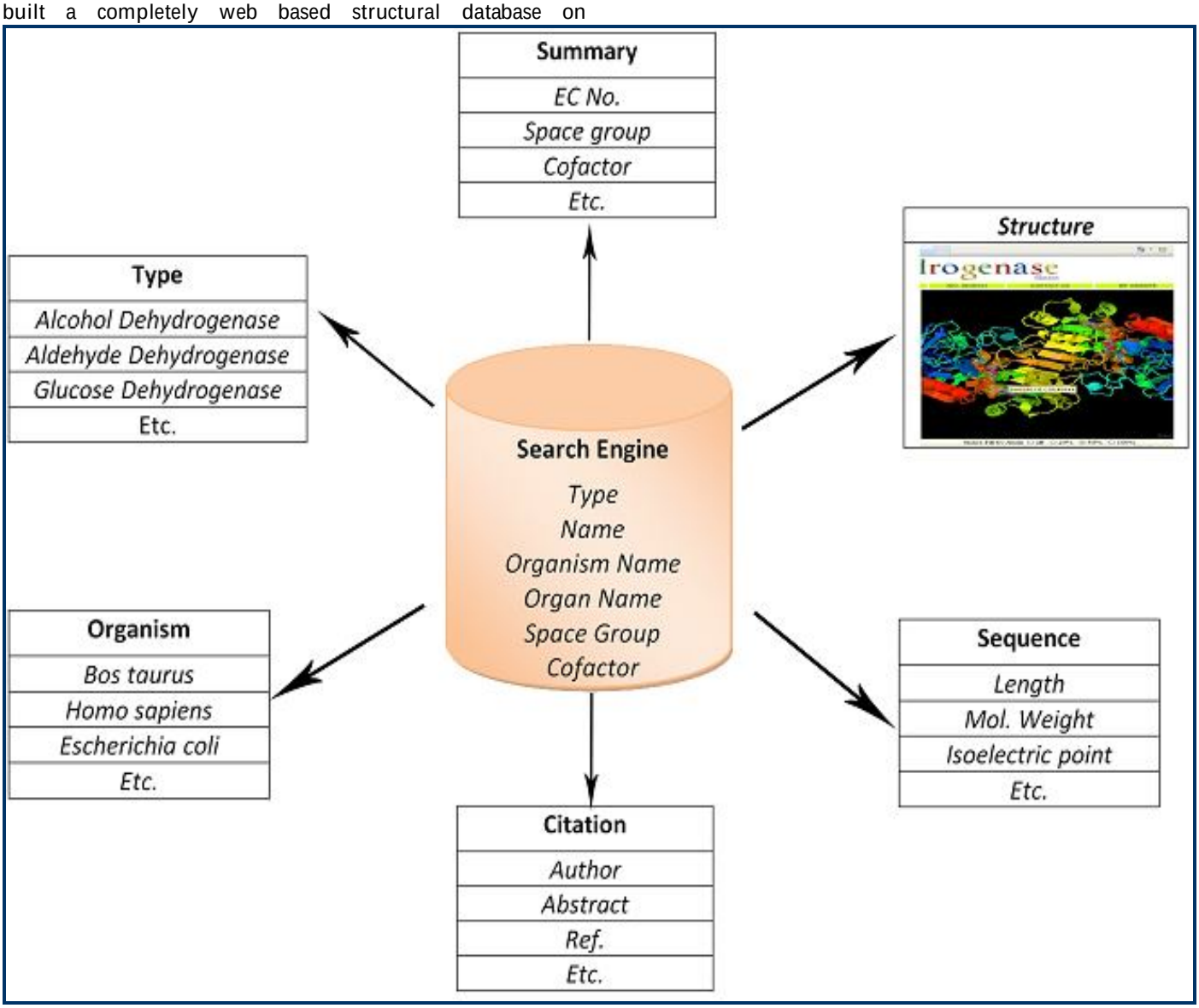

Figure 1: Data organization for DB Dehydrogenase.

Data collection and validation:

All the data were initially collected from Protein Data Bank (PDB), **[11]** and validated with UniProt Protein Knowledgebase **[12].** To reclassify in a better way; we considered the sequence, domain architecture, protein affinities, binding mechanisms, cofactors, substrates, inhibitors and products. For these we dealt with various web resources like NCBI [**13**] followed by BRENDA, **[14]** PDBsum, **[15]** KEGG, **[16]** IUBMB**, [17]** MetaCyc, **[18]** SYSTERS, **[19]** PRIAM, **[20]** InterPro **[21]** and published literatures.

Data Access and Generation:

The database interfaces include: Home (general information), Advanced Search (a combined multiple search), Basic Search (by name, organ, organism, co-enzyme, keyword), Classification (by enzyme class, organism), External Links

(cross-reference) and Help (guide to database). The implementation of a menu-based bespoke search system allows the user to perform either a broad or user specific search from one simple search interface. The organizational framework in DB Dehydrogenase is designed in a manner to help users in easy navigation and retrieve information from database (**Figure 1).**

Utility to the biological community:

Proper classification of dehydrogenase enzyme was always been a hectic job due to multiple substrate affinity, manifold cofactor resemblance, multiple functional domains etc. We have developed a coherent system of classification by considering each enzyme class with reference to its substrate binding sites. The annotating method, we have used is quite appropriate for better classification of dehydrogenase enzymes. The data contained in DB dehydrogenase is compiled manually from previously published peer reviewed articles and verified, where possible, from the original literature. This suggests that, compared to other databases, it will be more accurate and reliable.

Caveats:

We would like to mention, initially, as with all databases, random errors may occur due to human slip-up during the data accumulation or due to error within the original experimental data. Intimations to the authors for these kinds of mistakes will be highly appreciated.

Future Development:

In future we plan to add an option to show the recently published articles on dehydrogenase and to update and improve the database in regular time interval.

Acknowledgment:

The study was supported by grants from DBT, Ministry of Science & Technology, Govt. of India, New Delhi.

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Edited by P Kangueane
Citation: Nandy *et al*. Bioinformation 8(20): 1000-1002 (2012)