

# Fold-Function Relationship of PLP-Dependent Enzymes

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## 1 Introduction

Empirical relationships between the three-dimensional structures of enzymes and their functions will provide powerful tools for deducing functions from structures. Such relationships exist at different levels of protein three-dimensional structures from local structural motifs to global fold. We have proposed a novel relationship, "fold-based superfamily", based on global fold and reaction mechanism of enzymes [1]. The relationship was successfully applied to ATP-related enzymes that are evolutionarily more distant than superfamilies, where we defined the global folds of ATP-binding domains by the  $\beta$ -sheet topology and the functions by reaction mechanisms.

Here we report the results that we analyzed the global fold-function relationships of the enzymes using pyridoxal phosphate (PLP) as a coenzyme.

## 2 Method and Results

### 2.1 $\beta$ -topology groups of proteins and a network of kinship 1 relations

We introduce the concept of a network of kinship relations, which is intended to locate essentially all  $\beta$ -sheet-containing protein domains [1]. We focus our attention on  $\beta$ -sheet topology, i.e., the directions of individual  $\beta$ -strands and their connectivity. The kinship relations among various  $\beta$ -sheet topologies are defined based on *the assumption* that predominant elementary event leading to the creation of a new  $\beta$ -sheet topology during the molecular evolution is either the addition or deletion of one  $\beta$ -strand at the edge of an existing  $\beta$ -sheet. Such a group is defined here as a  *$\beta$ -topology group*. We classified the global folds of the non-homologous domains into 428  $\beta$ -topology groups.

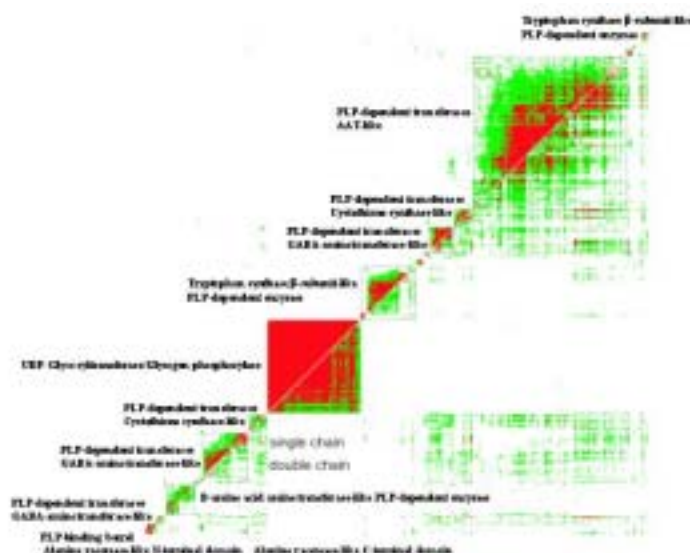
We defined the kinship relations among the  $\beta$ -topology groups, based on the assumption described above. A pair of  $\beta$ -topology groups, related by the deletion or addition of one  $\beta$ -strand at the edge of a  $\beta$ -sheet, is defined as having the first degree of kinship, kinship 1. Then we constructed a network of kinship 1 relations.

### 2.2 Fold-function relationships of PLP-binding domains

We searched the LIGAND chemical database for enzymatic reactions in KEGG and found 395 PDB entries for 39 enzymes that use PLP as a co-factor in their catalytic reactions. These enzymes distribute in 50 sequence families and 7 SCOP superfamilies. PLP-dependent enzymes in a superfamily have the same

$\beta$ -topology group; 39 PLP-dependent enzymes are grouped into only 7  $\beta$ -topology groups. These  $\beta$ -topology groups are far from each other on the network of protein kinship relations; no evolutionary relation is found among the PLP-dependent enzymes. Eliot and Kirsch defined 7 different functions for the PLP-dependent enzymes based on their reaction mechanisms considering stereo-specificity [2,3]; one reaction mechanism for one superfamily.

**Figure 1. Result from the all-against-all comparison among the 395 PLP-binding sites are summarized in the correlation map by Compl program [4].**



Next, we analyzed the relations between local structures, PLP-binding sites, and functions of the PLP-dependent enzymes by using Compl program [4] that searches a common structural motif in the PLP-binding sites. Each superfamily has an independent local structural motif (Figure 1). This is the first analysis of the relationship between local structures and reaction mechanisms of PLP-binding sites.

### 3 Discussions

Two types of empirical relationships between protein structures and functions appear to exist. The first is between local structures and functions, and the other is between global folds and functions. Although the mechanisms of enzymatic reaction are likely to explain the former type of relationship, such direct mechanisms to explain the latter type are rather difficult to elucidate. The latter type of relationship may have its origin in molecular evolution. Mechanisms may exist only indirectly behind the conservation of global folds and their associated functions.

We analyzed the empirical relationships of the PLP-dependent enzymes at two levels of three-dimensional structures; relationships between  $\beta$ -topology groups (global fold) and reaction mechanisms of PLP, and those between common structural motifs (local structure) and reaction mechanisms. Both of the two levels of empirical relationships between global-structures and functions, and local-structures and functions gave the same results for PLP-related enzymes. 39 PLP-dependent enzymes having 7 categories of reaction mechanisms in 7 SCOP superfamilies were classified into 7 independent fold-based superfamilies and 7 independent common local structures. In ATP-binding domains, 75 different enzymes having 5 categories of reaction mechanisms in 32 SCOP superfamilies were classified into 29 independent fold-based superfamilies [1]. In conclusion, PLP-enzymes are likely evolved from 7 independent ancestors.

### References

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