A New Phylogenetic and Sequence Analysis of metallo-*beta*-Lactamases

Sheuli Zakia, Cristina C. Clement, Janet Gonzalez, Sandy Zhang, and Manfred Philipp

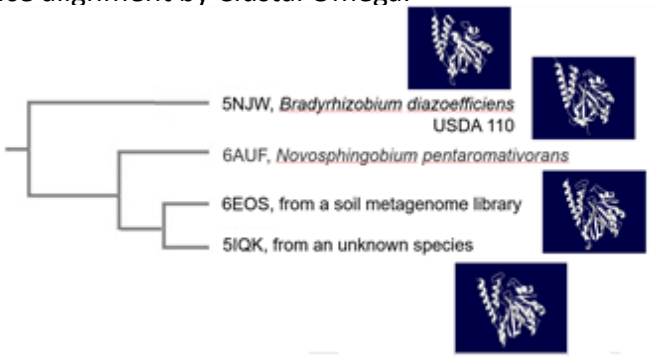
Laredo College, Weill-Cornell Medical Center, LaGuardia Community College, the Bronx High School of Science, Lehman College & the Graduate Center, City University of New York

Metallo-*beta*-lactamases are important causative agents of bacterial resistance to *beta*-lactam antibiotics. In contrast to lactam resistance associated with Class A, C, and D beta-lactamases, there is a paucity of clinically-accepted treatments for lactam resistance that is related to the expression of metallo-*beta*-lactamases.

Metallo-*beta*-lactamases (Ambler Class B) are generally quite uniform among very different bacterial species, indicating rapid spread of their genes among those species. One hundred protein structure depositions are available for the NDM-1 beta-lactamase, an enzyme expressed by human pathogens. However, the VAST database shows that there are many other closely related structures in the pdb databases that show very high three-dimensional positional alignment values (over 200 out of 231 amino acids) but very low sequence identity. These variant proteins show positional RMS deviations as low as 1.9 Angstroms at as little as 22% sequence identity, an RMS value close to the experimental error of the structure determinations. This study examines the structural variations and phylogenetic relationships among these proteins.

Structural Constancy Despite Sequence Variation

These images are derived from selected soil-based metallo-*beta*-lactamases that are structurally homologous to the NDM-1 lactamase expressed by pathogenic bacteria.
Protein sequence alignment by Clustal Omega.

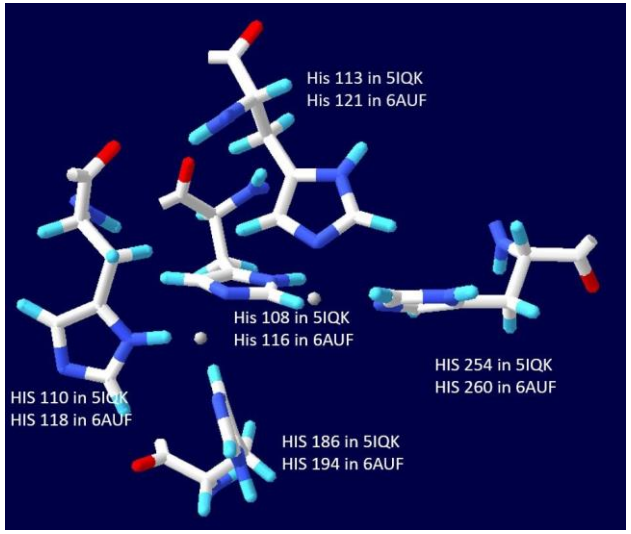


VAST Structural Homology to NDM-1

Selected VAST Results for Structural Homology to the NDM-1 Enzyme

PDB Identifier	RMSD	Aligned Residues	Sequence Identity
5NJW	2.94 Å	190	17%
6AUF	2.49 Å	183	16%
6EOS	2.56 Å	184	15%
5IQK	2.74 Å	188	14%

The active sites of the enzymes discussed here contain five histidine residues complexed to two zinc ions. (NDM-1 has four histidines, one Zinc and one Cadmium ion.)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3212353/
These residues overlap within experimental error.



References:

The VAST Structural Database:
https://www.ncbi.nlm.nih.gov/Structure/vastplus/vastplus.cgi?uid=5ZGE
Clustal Omega, Protein Sequence Alignment:
https://www.ebi.ac.uk/Tools/msa/clustalo/
Swiss PDB Viewer: https://spdbv.vital-it.ch/
PDB Databases: https://www.rcsb.org/ and
https://www.ncbi.nlm.nih.gov/Structure/index.shtml