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Research Article

Bioinformatic analysis of metal transportomes from *Mycobacteria* Sp.

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Abstract

Mycobacterium is immovable induce aerobic, acid-fast gram-positive bacilli with high genomic content (59-66%). In the operon structure frequently establish for the genes of three molecular components: the ABC-binding protein, the membrane protein, and the substrate-binding protein, the rates of multidrug resistant and metal ions. The main objective of this study was to analyze the metal ions from five *Mycobacterium* species and to identify the metal transporters with "Genomic Island" associated features, *in-silico* analysis allowed identification of metal and drug transporters, phylogenetic analysis, genomic island path analysis, prediction of interacting metal ions, 3D structure, domain analysis and for the NiCoT metal transporter from *Mycobacterium tuberculosis*. These data are the first results of a big frame project that aims to accelerate the prioritizing of gene candidates that control element accumulation by taking advantage of high-throughput. The present *in-silico* study reveals the complete suite of NiCoT Metal Transporter in *Mycobacterium tuberculosis* H37Rv, which is involved in urease enzyme activity and biological function. The STRING analysis defines that the functional partners involved in transport of metal ions. While high expression yields of membrane proteins remain significant bottleneck for many proteins.

Introduction

In recent years the complete genome sequences of versatile organisms from the three domains of life are rapidly accumulating. It is now possible to attempt to reconstruct and analyze a complete set of biochemical reaction pathways that an organism adopts, especially on the transport, synthesis, and degradation of specific chemical compounds [1]. Through comparative studies, metal ions play a life preserve role in prokaryotic metabolism [1-3]. Biological management of metal ions is skilled by a complex interplay between metal ion and drug transporters (transmembrane importers, transmembrane exporters) and their regulatory components [1-5]. *Mycobacteria* belong to the family *Mycobacteriaceae* and are members of the CMN group (*Corynebacteria*, *Mycobacteria and Nocardia*). The families *Mycobacteriaceae* are gram-positive, immobile, catalase-positive have a rod like to filamentous morphology and it could be pleomorphic. As a group, they produce characteristic long chain fatty acids termed mycolic acids. *Mycobacteria* are acid-fast rods of variable appearance, approximately 0.2 - 0.6 by 1-10 mm. The genus *Mycobacterium* consists of 127 species according up to the minute approved list of bacterial species [3]. *Mycobacteria* arranged into four groups according to the Runyon classification: a) Photochromogens: slow growers and form pigment when exposed to light. (e.g.: *M. kansasii*, *M. marinum*, *M. simiae*). b) Scotochromogens: slow growers and form pigment in the dark (e.g.: *M. scrofulaceum*, *M. szulgai*, *M. gordonae*). c) Non-photochromogens: slow growers and not pigmented (e.g.: *M. malmoense*, *M. xenopi*, *M. avium*-complex, *M. ulcerans*, *M. haemophilum*). d) Rapid growers: fast growers (e.g.: *M. fortuitum*, *M. chelonae*, *M. abscessus*). Most slow-growing species have been associated with disease in humans while only few species of group 4 are disease associated [6,7]. The identification of a new species was conventionally based on the description of the Runyon classification, the biochemical properties of the strain(s) and the degree of DNA-DNA hybridization. Taxonomically, *Mycobacteria* are the single genus within the family of *Mycobacteriaceae*, in the order *Actinomycetales*. It includes pre-nominal micro-organisms and they are traditionally differentiated on the basis of phenotypic

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characteristics, culture properties that help to separate among various species of *Mycobacteria*. It is also a leading cause of infection in various domesticated animals and wildlife. The *Mycobacterial* cell envelope, which is an analyzable tripartite structure containing a high proportion of lipids (approximately 30% to 40% of the total weight) could play an essential role in the adaptation of *Mycobacteria* to intracellular growth and survival, immune modulation and drug resistance [7]. The availability of complete genome sequences of five species namely *M. avium* K10, *M. leprae* AF2122, *M. bovis* 97, *M. tuberculosis* H37Rv, *M. smegmatis* str. MC2155 provided an opportunity to analyze the metal transporters and multidrug transporters [8-22]. Secondary transporters from the NiCoT family are able to uptake either both Ni and Co, or prefer only Ni ions. NiCoT's are widespread among bacteria and found in some Archaea and fungi. Substrate preferences correlate with the genomic localization of NiCoT genes adjacent to clusters of Ni/Co - dependent enzymes and enzymes of B12 biosynthesis, as well as with the presence of Ni or B12 regulatory sites upstream [4,5,23-35].

Methods

Compilation of metal and multidrug transporters

The genome sequence information of five sequenced species *M. avium* K-10, *M. leprae* AF2122, *M. bovis* 97, *M. tuberculosis* H37Rv, *M. smegmatis* str. MC2155 in this study were selected from transport database (33). Transport database is a relational database describing details of a comprehensive IUBMB approved classification system for transport proteins known as classification of enzymes. TCDB is freely web accessible at http://www.tcdb.org, curated relational database and also containing protein sequence, classification, structural, functional and evolutionary information about transport systems from a variety of living organisms. It offers several tools specifically designed for analyzing the unique characteristics of transport proteins and serves as a genome transporter annotation tool. In order to search for homologs of a transporter family the best-composed hit was used in a subsequent BLASTP search against the five species whole protein sequences and retrieved the members. From the compiled sequences phylogenetic trees were constructed for substrate specific transporters individually and through analyzing the aligned sequences conserved domains for individual metal ion and drug transporter were reported, protein search was also carried out with retrieved homolog's using CLC sequencer database version 6.9.1 [10]. For some of the specific nickel secondary transporter and cobalt transporters orthologous and paralogous sequences were obtained using KEGG database and phylogenetic trees were generated for them (KEGG database). Transmembrane helix prediction for the membrane transporters was performed using Transmembrane Hidden Markov Model (TMHMM) version 2.0. Genomic location and gene organization search was carried out using ISLAND PATH analysis [4,5,12,35].

Protein sequence analysis

CLC workbench has employed to analyze the metal transporter and multidrug transporter proteins [10]. The protein sequences were collected and aligned to identify regions of similarity that may be a consequence of functional, structural or evolutionary relationships between the sequences. Conserved domains are identified by using Motif Search in KEGG database. The conserved motif in the ATP dependent transporter's membrane domain "LSGGQ" has been identified. This domain is the signature sequence for the ABC transporter proteins [4,5,10].

Phylogenetic analysis

Phylogenetic analysis is an illustration of the evolutionary relationships among a group of organisms. It was performed with the characterized prototypes using CLC protein workbench. For this analysis, Multiple Sequence Alignments (MSA) were produced using progressive alignment algorithm. The generated pair wise alignments were used for finding the evolutionary distance between the pairs. Pair wise distances thus calculated was used to create a Phylogenetic tree-employing Neighbor Joining (NJ) algorithm with 1000 bootstrap replicates [5,10].

Island path analysis

Mycobacteria species are ecologically diversified organisms habituated to grow in host-associated environmental conditions and some are multiple. In the five species named above except *Mycobacterium leprae* all are host-associated and it is multiple. Organisms to get acquainted to specific niche, they need to meet the requirements to survive in that conditions. Horizontal gene transfer mechanism is involved in the achievement of essential needs. Island Path Analysis was used for the detection of metal and drug transporters acquired through HGT. After generating the complete inventory of metal and drug transporters, we inspected the genomes of five *Mycobacterium* species with island path software (IPA version 1.0 tool) for the identification of those transporters located in GI's or exhibiting GI associated features like anomalous %G+C, dinucleotide bias above 1 STD DEV, presence of RNA genes (tRNA, rRNA genes) and mobility genes (transposons, insertion sequences). A pre-nominal GI can be identified with certainty by the presence of eight or more consecutive ORF's with dinucleotide bias alone or dinucleotide bias plus a mobility gene in proximity [1].

Identification of metal ion transporters and their sub cellular localization

The protein transporter has transmembrane helices which are identified using a tool TMHMM (Trans Membrane prediction using Hidden Markov Models) an option present in Transport DB. The transporters with transmembrane helices are then subjected for the identification of protein sub cellular localization using PSORTdb (http://db.psort.org/). It is a web accessible database of SCL for bacteria that contains both information determined through laboratory experimentation and computational predictions [12].

Prediction of interaction and interacting partners of the metal ion transporters

The Nickel & Cobalt metal transporters are the major constituents in urease enzyme & many biological functions. The protein-protein interactions are studied using STRING

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database (http://string-db.org/). It is pre-computed global resource for the exploration and analysis of the associations. Since the evidence differs conceptually, and the number of predicted interactions is very large, it is essential to be able to assess and compare the significance of individual predictions. Thus, STRING contains a unique scoring-framework based on benchmarks of the different types of associations against a common reference set, integrated in a single confidence score per prediction [5,14].

Prediction of 3D structure and domain analysis

After STRING analysis, the NiCoT transporter which is involved in transport of Nickel efflux are subjected to Homology Modeling and their 3D models are generated by selecting the reliable template using Swiss-Model (http:// swissmodel. expasy.org/) [15]. The SWISS-MODEL template library provides annotation of quaternary structure and essential ligands and cofactors to allow for building of complete structural models, including their oligomeric structure. The 3D structures that were built are subjected for verification using RAMPAGE (http://mordred. bioc.cam.ac.uk) and active domains are analyzed using ProDom (http://prodom.prabi.fr) [1].

Results

From genome to metal and drug transportome

Based on the global features of five *Mycobacteria* genomes we could draw a comparison among the genome size, total number of genes, transporter proteins, G+C content (%), total number of metal transporters, total number of drug transporters (Table 1). As shown in the table 1, *M. smegmatis* has largest genome size and *M. leprae* has smallest genome size in comparison. Among the total metal and drug transporters *M. smegmatis* has the highest number of proteins when compared with *M. leprae*.

Based on membrane transporter database (Transport DB), we have compiled the metal and drug transportomes for the alkaline earth metal (Mg^{2+}), transition metal ions (Zn^{2+}, Mn^{2+}, Cu^{2+}, Ni^{2+}, Co^{2+}), and heavy metal (Cd^{2+}) in five species of *Mycobacteria* (Table 2).

From the above analysis, as shown in Table 3, we were reported that *M. smegmatis* has the highest number of ATP dependent transporters (12 ATP dependent metal & 28 drug transporters) among the group and secondary metal transporters are high *in M. avium* [7] and drug transporters in *M. smegmatis* (128). Ion channels and also the unclassified transporters are very less in number in all the group members and they are identified in metal transporters.

Salient features of metal and multidrug transportomes

Apart from the Transporter Database the protein information is provided in *Mycobacterium* database as well as in Transport DB of Tuberculosis Database. The up to date information is maintained and updated if any new protein is identified. The metal ion transporters and multidrug transporters are identified in all five species mentioned above and conserved motif domains are also identified for these respective species. Dataset cataloguing and multiple sequence alignment of the sequences helped us to find the unique signature sequences (Figure 1). The major finding of our study is that there are only

Table 1: Global features of five representative *Mycobacteria* species.

Topology	*M. avium K-10*	*M. bovis* AF2122/97	*M. leprae*	*M. tuberculosis* H37Rv	*M. smegmatis* MC2155
Genome size(bp)	4829781	4345492	3268203	4411532	6988209
G+C content (%)	69.39	65.47	59.70	65.47	67.48
Total no. of genes	4350	3920	1605	3999	6716
Total Transporter Proteins	170	153	56	148	423
Total Metal Transporters	23	20	7	12	42
Total drug Transporters	27	26	3	31	156
Selected Metal Transporters	19	14	6	11	19

Table 2: Comparative analyses of Metal Transporters.

Metal Transporter Type/ Family	Number of Transporters				
	M. avium	*M. bovis*	*M. leprae*	*M. tuberculosis*	*M. smegmatis*
ATP- Dependent	11	9	3	8	12
ATP-Binding Cassette (ABC Superfamily)	9	4	2	2	9
P-type ATPase (P-ATPase) Superfamily	2	5	1	6	3
Ion Channels	1	1	1	0	2
CorA Metal Ion Transporter	1	1	1	0	2
Secondary Transporters	5	2	2	1	2
Ni^{2+} Co^{2+} Transporter family	1	1	0	1	0
Metal Ion Transporter family (Nramp)	4	1	2	0	2
Unclassified transporter	2	2	0	2	3
Mg^{2+} Transporter-E family	2	2	0	2	2
Peptidoglycolipid Addressing Protein (GAP) family	0	0	0	0	1

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three Nickel transporters from three species found among all the organisms from the ground and it is secondary transporter belongs to $Ni^{2+}Co^{2+}$ transporter family. We have mainly focused on Nickel-Cobalt metal ion transport and multidrug transporters. The nickel-cobalt metal ion is identified in three species of selected five species (Figure 2). It is identified in *M. bovis* (Mb2881), *M. tuberculosis* (Rv2856) and *M. avium* (MAP2924). As of now up to date the main motif is identified in Nickel-Cobalt is "HAFDADH" in second transmembrane helix. But when compared to these three species we have identified

Table 3: Comparative analyses of drug transporters.

Multidrug Transporter Type/Family	No. of transporters				
	M. avium	*M. bovis*	*M. leprae*	*M. tuberculosis*	*M. smegmatis*
ATP-Dependent family	11	8	2	10	28
ATP-Binding Cassette (ABC) Super family	11	8	2	10	28
Secondary Transporter	16	18	1	20	128
Drug/Metabolite Transporter family	2	0	1	1	15
Major Facilitator Super family	14	18	0	18	95
Resistance-Nodulation-Cell division (RND) Super family	0	0	0	0	17
MOP Super family	0	0	0	1	1

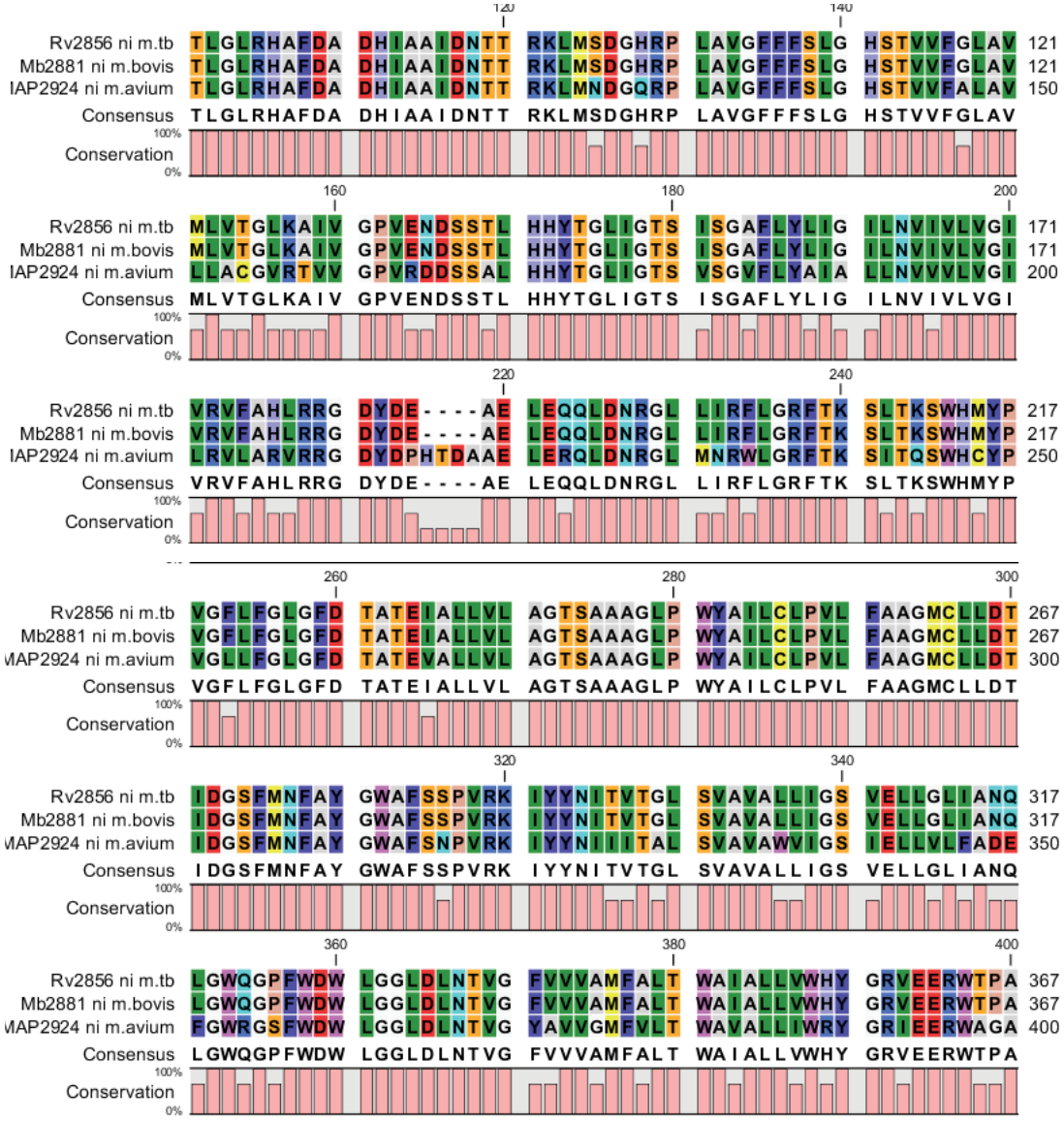

Figure 1: Multiple sequence alignment of nickel transporters from *M. avium, M. bovis, M. Tuberculosis*.

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the main motif "HAFDADH" in third transmembrane helix and also other three conserved motif regions are identified in sixth, seventh and eighth peaks of transmembrane helix. The proteins were collected and by using Motif search from KEGG database motifs are identified and by using TMHMM version 2 software the conserved domain motifs are confirmed by analyzing the transmembrane helix regions (Figure 1). "VGFLFGLGFD" – in sixth peak, "IDGSFMNAYGWAFS" – in seventh peak and "LGGLDLNTVG"- in eighth peak. In fourth and fifth transmembrane helix the conserved motifs are identified but around 95% identity. In these two conserved domain motifs one of the amino acid sequence is 99% identity. "SSTLHHYTG"- in fourth peak and "LEQQLDNRGL" – in fifth peak.

The multidrug transporters are aligned using CLC Workbench Software and ClustalW and Phylogenetic tree is also constructed (Figure 2). Horizontal gene transfer effect plays an important role in the acquisition of the requirements to adapt to specific niche conditions. Island path analysis tool is used to analyze Genomic island associated features of metal ion transporters for 5 *Mycobacterial* sp. Thus, island path analyzer gave us the clear idea on the number of metal ion transporters acquired through HGT mechanism in the *Mycobacterial* sp. [34]. The NiCoT (Rv2856) metal transporter with its sub cellular localization is identified from Transport DB and PSORTdb respectively (Figure 3). From the above-mentioned data, the protein is subjected to STRING analysis and their interactions and interacting partners are identified. The interactions indicate their functional protein partners are involved in the mechanism of transport of metal ion are interacting with each other (Figure 4). STRING database analyzed protein is subjected to Homology Modeling & 3D structures are relied which are generated using the template from Swiss Model tool (Figure 5). The structures are validated using RAMPAGE (Figure 6) and its function & domains are identified using PRODOM. From this

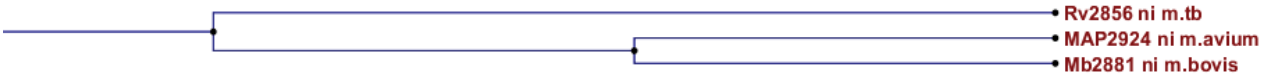

Figure 2: Phylogenetic tree construct of nickel transporters from *M. avium, M. bovis, M. tuberculosis* using CLC Workbench Software.

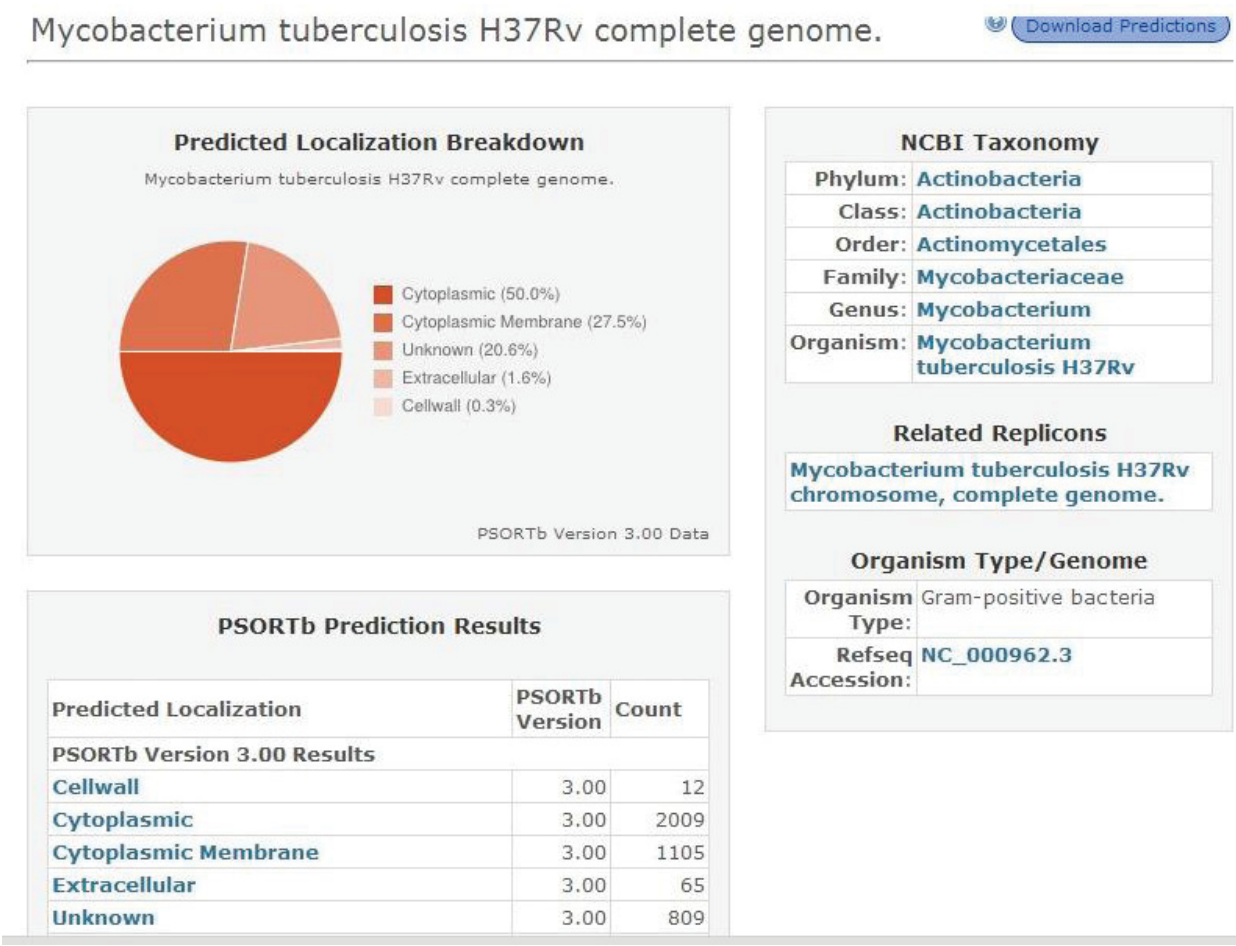

Figure 3: NiCoT (Rv2856) metal transporter with its sub cellular localization is identified by using PSORTdb.

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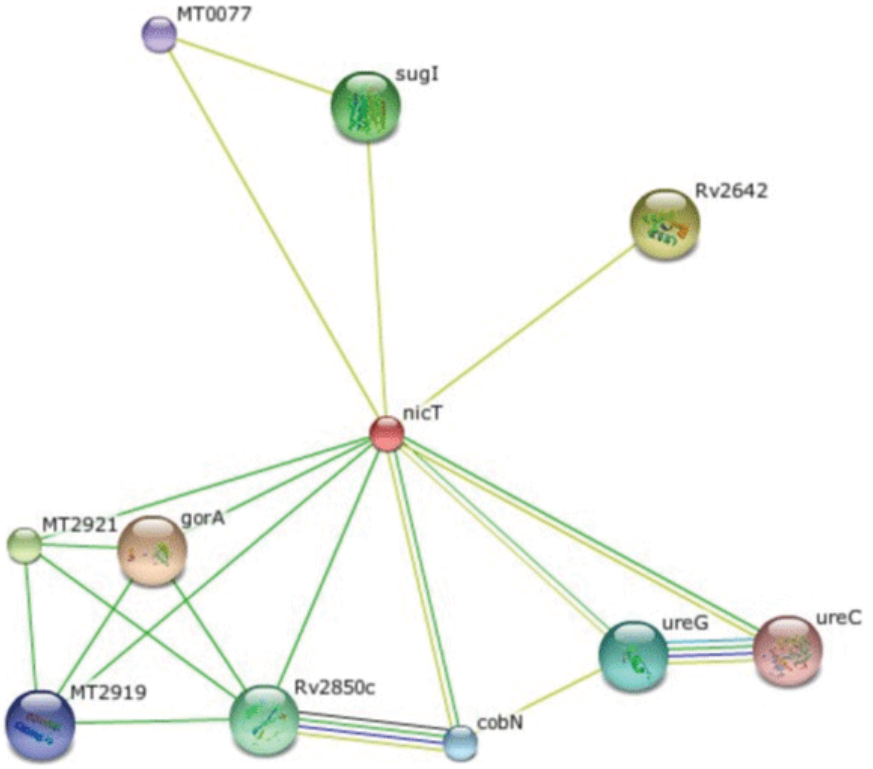
analysis it is clear that the NiCoT protein transports the metal ion as their functional domain is Secondary Transporter.

Discussions

In this study we have performed a dataset cataloguing for 69 metal and 243 drug transporter proteins from five *Mycobacterial* sp. This is the comprehensive genomic comparison of metal transporters, providing potentially important insights into the fundamental molecular aspects and novel facets of *Mycobacterial* metal transporters. Transition metals nickel and cobalt are essential components of many metalloenzymes. Ni-dependent enzymes are urease, [NiFe] hydrogenase [Ni] superoxide dismutase, CO dehydrogenase, and methyl-CoM reductase. In the form of coenzyme B12, cobalt plays a number of crucial roles in many biological functions. Also, there are some noncorrin-cobalt-containing enzymes (e.g. nitrile hydratase). Synthesis of Ni / Co enzymes and coenzyme B12 requires high-affinity uptake of the metal ions from natural environments where they are available only in trace amounts. Ni and Co uptake in bacteria is mediated by various secondary transporters and by at least two different ATP-Binding Cassette



This is the **evidence view**. Different line colors represent the types of evidence for the association.

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(requires Flash player 10 or better)

Your Input:

		Neighborhood	Gene Fusion	Cooccurrence	Coexpression	Experiments	Databases	Textmining	[Homology]	Score
nicT	nickel-transport integral membrane protein (372 aa) *(Mycobacterium tuberculosis H37Rv)*									

Predicted Functional Partners:

gorA	mycothione reductase (459 aa)	•								0.700
Rv2642	ArsR family transcriptional regulator (126 aa)							•		0.653
MT2921	hypothetical protein (346 aa)	•								0.623
sugI	sugar-transport integral membrane protein SugI (502 aa)							•		0.605
Rv2850c	magnesium chelatase (629 aa)	•								0.570
ureG	urease accessory protein UreG; Facilitates the functional incorporation of the urease nickel me [...] (224 aa)	•						•		0.542
cobN	cobaltochelatase subunit CobN (1194 aa)	•						•		0.514
MT2919	PE-PGRS family protein (615 aa)	•								0.475
MT0077	maturase (235 aa)							•		0.469
ureC	urease subunit alpha (577 aa)	•						•		0.443

Figure 4: NiCoT associated proteins identification by STRINGE analysis.

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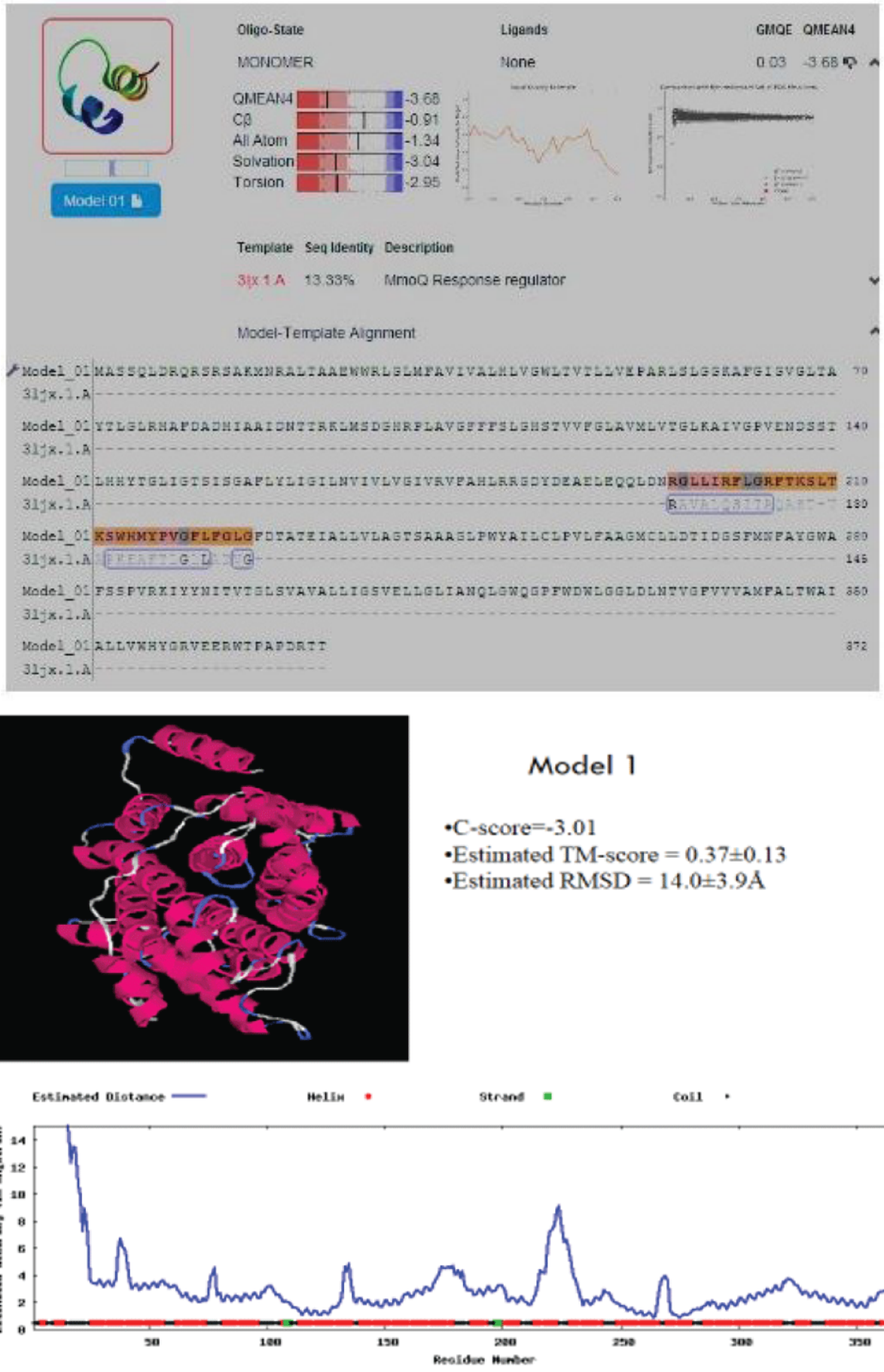

Figure 5: Homology modelling data.

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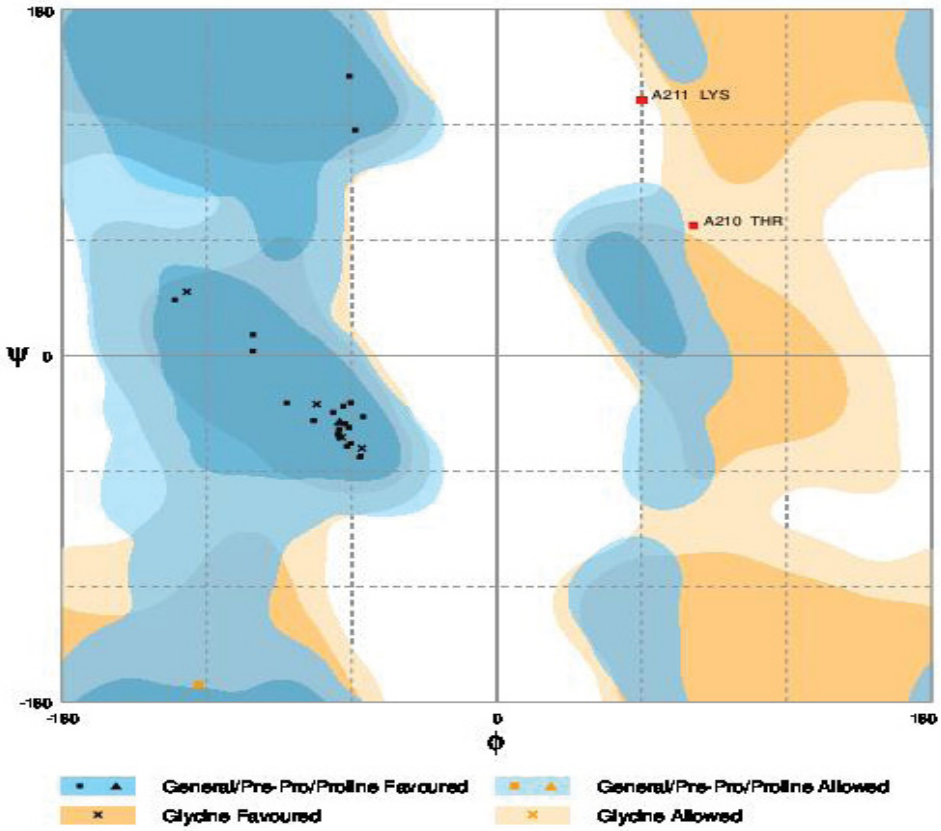

Figure 6: Rampage Validation.

(ABC) systems. It is thought to be involved in transport of nickel across the membrane responsible for translocation of substrate across membrane. For the urease enzyme activity nickel metal ion is used as a co-factor and vitamin B12 enzyme activity cobalt ion is used as a co-factor. The present *in-silico* study reveals the complete suite of NiCoT Metal Transporter in *M. tuberculosis* H37Rv, which is involved in urease enzyme activity and biological function. The STRING analysis defines that the functional partners involved in transport of metal ions.

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