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# *IN SILICO* FINDING OF THE PUTATIVE DRUG TARGETS FROM HYPOTHETICAL SET OF PROTEINS FOR *MYCOBACTERIUM LEPRAE* TN

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**Keywords:**

Leprosy, *Mycobacterium leprae*, Hypothetical protein, Inositol metabolic pathway, Putative drug target

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**ABSTRACT:** Leprosy is a chronic granulomatous disease caused by acid-fast bacilli *Mycobacterium leprae*. It is most prevalent in tropical countries and poses a threat to over 122 countries across the globe. In 2012, 232857 new cases of leprosy were registered in the world. World Health Organization (WHO), recommended the Multi Drug Therapy (MDT) for treatment of leprosy, but the minimum duration of treatment ranges from 6-12 months. Therefore, the need of a new putative target for treatment of leprosy, which is effective in leprosy and reduces the duration of treatment. The Proteome information available suggests that among the 1603 proteins in *M. leprae* TN, a staggering 27% or more remains classified as hypothetical uncharacterized set of proteins. In this present work we, assign the probable functions of hypothetical set of proteins present in *M. leprae* to explore their plausible role as new putative drug targets. Out of 442,177 hypothetical protein sequences had GO term. Of these, 43 sequences had disease ontology (DO) term, 59 sequences had human phenotype (HP) term and out of these 43 sequences, 16 sequences were found to contain only DO term, while 27 sequences had both HP and DO term. Out of 177, 15 sequences were found to be associated with 39 KEGG reference pathway pathways. Out of 39 pathways, inositol phosphate metabolism, fatty acid degradation, ethylbenzene degradation, sulfur relay system and limonene & pinene degradation were common metabolic pathway, which might be used as putative drug target for *M. leprae*.

**INTRODUCTION:** Leprosy is a chronic granulomatous disease and is also known as Hansen's disease (HD) [1]. The disease is caused by an acid-fast, rod-shaped bacillus *Mycobacterium leprae*. The clinical manifestations of leprosy are bacillary infiltration, lesions on skin, peripheral neuropathy and various immunological reactions.[2] It is an endemic disease and is spread out in tropical counties.

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According to the World Health Organization (WHO) more than 115 countries were affected by leprosy, and around 189018 prevalent cases were registered till the first quarter of 2013 [3]. Moreover, 232857 new cases of leprosy per 100000 populations were registered during 2012. The regional distribution of the disease is given in **Table 1**. Overall 25 countries of the African region, 28 Americas region, 20 Eastern Mediterranean regions, 11South-East Asia region and 31 countries of the Western Pacific region were included. However, 134752 new cases were reported in India in the year 2012 [3]. The number of cases in 2012 was higher as compared to the cases reported in recent years as shown in **Fig. 1**.

Leprosy is a Flügge droplet infection, transmission occurs by inhalation of the bacilli contained in nasal secretion, but other possible route of transmissions of leprosy are skin erosions, blood, vertical transmission, breast milk, and insect bites [4]. The incubation period of leprosy is about 3-10 years, symptom disabilities when, *M. leprae* invades Schwann cells in the peripheral nervous system leading to damage of peripheral nerve.[1] The main symptom of leprosy is disfiguring skin sores, lumps or bumps with loss of pain and sensation due to damage of peripheral nerve.

In 1982, the WHO classified leprosy, based on the bacterial index (BI). It becomes paucibacillary (PB) when BI goes lower than 2 and multi-bacillary (MB) when BI increases more than or equal to 2[5]. WHO campaign for leprosy with the support of private foundations and pharmaceutical companies was for the recommendation of Multi Drug Therapy (MDT) [6]. Now-a-days, genome sequencing provides fast and reliable solutions to identify the whole information of the genome. The genome sequencing of *M. leprae* samples from Tamil Nadu, India was performed by Cole *et al*. in the year 2001 using a combination of sequenced cosmids from multiplex sequencing and end sequences from the genome shotgun library using dye termination on automated sequencers. *M. leprae* TN genome belongs under SNP type 1 and subtype A. The molecular weight of the genome is 2.2 x 109 Daltons, containing 3,268,203 base pairs (bp) and G+C (guanine + cytosine) content of 57.8%. The genome contains 49.5% of total genome as protein-coding gene, 27% of pseudo genes and remaining 23.5% of genome does not show any expression [7]. The total 1603 proteins are available in different protein database out of them, 442 protein sequences are hypothetical and uncharacterized.

Hypothetical proteins are plausible target for drug discovery by computational methods. Literature survey suggested that hypothetical proteins assign the functional information in various organisms by computational methods. Computational analysis of hypothetical proteins for human fetal brain showed that many hypothetical proteins have ligase activity [8] No prior comprehensive studies were undertaken on hypothetical proteins for *M. leprae* TN, therefore functional annotation and detailed investigations of hypothetical proteins, which might be used as putative drug targets for *M. leprae* TN, has been attempted in the present work.

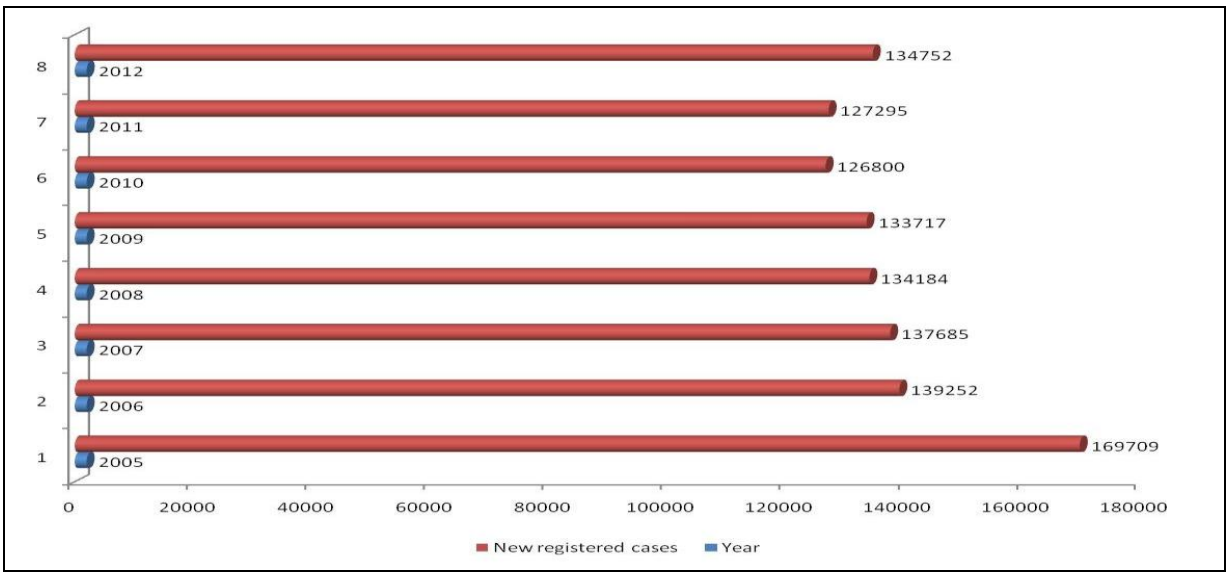


**FIG. 1: REPORTED CASE OF LEPROSY ACROSS THE GLOBE**

**TABLE 1: WHO REPORT ON THE PREVALENCE OF LEPROSY?**

| S. No | Territory | Registered prevalence | No. of new cases during (2012) |
|---|---|---|---|
| 1 | African | 17540 | 20599 |
| 2 | Americas | 33926 | 36178 |
| 3 | Eastern Mediterranean | 4 960 | 4235 |
| 4 | South-East Asia | 125167 | 166445 |
| 5 | Western Pacific | 7425 | 5400 |

## METHODOLOGY:

## MATERIALS AND METHODS:

**Databases employed:** Uncharacterized hypothetical protein sequences for *Mycobacterium leprae* TN were retrieved from Proteome sets of UniProt-KB database [9]. Reference proteome set of *M. leprae* TN was last modified on July 4, 2014. Database of Essential Gene (DEG 10.6) was used for the investigation of essential gene present in *M. leprae* [10]. KEGG database (Release 69.0) was used to investigate the metabolic pathway information [11]. String Data Base (String DB, version 9.1) was used to identify and analyze the networks for Cluster of Orthologous Groups (COG) between protein families [12, 13].

**Tools employed**: Hmmscan web server was used to assign the Pfam domain information from the query protein sequences [14, 15]. CD batch search was used to assign the functional domain information from the query protein sequences [16]. dcGO web server was used to predict Genome Ontology (GO), Disease Ontology (DO) and Human Phenotype (HP) from the query protein sequences. [17] KEGG Automatic Annotation Server (KAAS) was used to predict pathway associations from the query protein sequences [18].

**Sequence analysis:** 442 hypothetical, uncharacterized protein sequences, belonging to *M. leprae*, were retrieved from UniProt-KB database. Domain information of these sequences was analyzed by hmmscan against Pfam database, with an e valve of $10^{-3}$. We found that out of 422, 318 protein sequences had at least one Pfam domain. Functional annotated conserved domain for 318 protein sequences were identified by NCBI Batch Web CD-Search against CDD--45746PSSMs with an e-value $10^{-3}$. We obtained 276 sequences, which had at least one functional annotated conserve domain. Further, these 276 protein sequences were analyzed for possible GO, DO and HP term. Out of 268, 177 sequences had GO term. KAAS was used to retrieve the reference metabolic pathway from KEGG for 177 sequences, which had GO term.

## RESULTS AND DISCUSSION:

**Sequence based drug target identification:** The proteome information available suggests that among the 1603 proteins in *M. leprae* TN, a staggering 442 remains classified as a hypothetical uncharacterized set. The result of Hmmscan suggested that out of 442 hypothetical uncharacterized hypothetical sequences, 311 sequences had at least one Pfam domain associated with the query sequences. After excluding spurious annotations, we predicted the functional annotated conserved domain from CD batch search for 311 sequences with an e value of $10^{-3}$, against conserve domain database (CDD). At last, we found 1685 functional annotated conserved domain which were widely distributed in 268 sequences.

Functional information related to Gene Ontology (GO) was predicted by domain-centric Gene Ontology (dcGO) predictor. The result of dcGO predictor was tabulated in supplementary **Table 1**. Out of 268 hypothetical/uncharacterized protein sequences, 177 sequences had GO term. Out of 177, 43 sequences had disease ontology (DO) term and 59 sequences had human phenotype (HP) term. Out of these 43 sequences, 16 sequences had only DO term, while 27 sequences had both HP and DO term.

## Supplementary:

**TABLE 1: FUNCTIONAL ANNOTATION OF 177 SEQUENCES HAVING GO TERM THROUGH DOMAIN-CENTRIC GENE ONTOLOGY (DCGO) PREDICTOR**

| Sl No. | UniprotKB ID | Gene Ontology (GO) | Human Phenotype (HP) | Disease Ontology (DO) | Homology with human proteome (Have DO term) |
|---|---|---|---|---|---|
| 1 | Q9CCZ0 | Phosphoric diester hydrolase activity | N/A* | N/A | N/A |
| 2 | Q9CBR0 | Protein complex scaffold | N/A | N/A | N/A |
| 3 | Q9CBF7 | Alcohol binding | N/A | N/A | N/A |
| 4 | Q9CBR1 | Adenylyltransferase activity | N/A | N/A | N/A |
| 5 | Q9CBQ9 | N-methyltransferase activity | Abnormality of the philtrum | N/A | N/A |
| 6 | Q9CBC7 | Exopeptidase activity | N/A | N/A | N/A |

| | | | | | |
|---|---|---|---|---|---|
| 7 | Q9CBR6 | Carboxy-lyase activity | N/A | N/A | N/A |
| 8 | Q50123 | Alcohol binding | N/A | N/A | N/A |
| 9 | Q9CBM5 | Phospholipid binding | Abnormality of metabolism/homeostasis | N/A | N/A |
| 10 | Q7APZ6 | Aminoacyl-tRNA ligase activity | N/A | Benign neoplasm | Negative |
| 11 | Q9CBR8 | Intramolecular transferase activity | N/A | Motor neuron disease | Positive |
| 12 | Q7AQ21 | N-acyltransferase activity | Abnormality of nervous system physiology | N/A | N/A |
| 13 | Q9CBI9 | Carboxylic ester hydrolase activity | Abnormality of lipid metabolism | Meningioma | Positive |
| 14 | Q7AQ25 | N-methyltransferase activity | Abnormality of the philtrum | N/A | N/A |
| 15 | Q9CBF8 | Hydrolase activity, hydrolyzing O-glycosyl compounds | N/A | N/A | N/A |
| 16 | Q9CBN4 | Monocarboxylic acid binding | N/A | N/A | N/A |
| 17 | Q9CBC4 | Small molecule binding | N/A | N/A | N/A |
| 18 | O33089 | Guanyl nucleotide binding | N/A | N/A | N/A |
| 19 | Q49857 | N-acyltransferase activity | Abnormality of the cerebral vasculature | N/A | N/A |
| 20 | Q49741 | ATPase activity, coupled to movement of substances | N/A | N/A | N/A |
| 21 | Q57240 | Oxidoreductase activity, acting on the aldehyde or oxo group of donors | N/A | N/A | N/A |
| 22 | Q49649 | Thiolester hydrolase activity | N/A | N/A | N/A |
| 23 | Q49755 | Carbamoyl-phosphate synthase activity | Hyperammonemia | N/A | N/A |
| 24 | Q49757 | Cysteine-type peptidase activity | N/A | Bullous skin disease | Negative |
| 25 | Q9CC91 | RNA polymerase II transcription factor binding transcription factor activity | N/A | N/A | N/A |
| 26 | Q9CC85 | Intramolecular transferase activity | N/A | N/A | N/A |
| 27 | P53425 | Catalytic activity | N/A | N/A | N/A |
| 28 | P53426 | Serine hydrolase activity | N/A | N/A | N/A |
| 29 | P50474 | Monooxygenase activity | N/A | N/A | N/A |
| 30 | O33011 | Purine NTP-dependent helicase activity | Abnormality of the outer ear | N/A | N/A |
| 31 | O33057 | Anion transmembrane transporter activity | Abnormality of movement | Pancreas disease | Negative |
| 32 | P54878 | Microbody | Abnormality of the musculature | N/A | N/A |
| 33 | P54581 | Intramolecular oxidoreductase activity | N/A | N/A | N/A |
| 34 | P54882 | Unfolded protein binding | Abnormality of the cerebral vasculature | N/A | N/A |
| 35 | Q9CD28 | Guanyl nucleotide binding | Paralysis due to lesions of the principle motor tracts | Autosomal recessive disease | Positive |
| 36 | O05668 | Intramolecular transferase activity | N/A | N/A | N/A |
| 37 | Q9CCW4 | N-methyltransferase activity | N/A | Connective tissue cancer | Negative |
| 38 | O32965 | Metallopeptidase activity | N/A | N/A | N/A |
| 39 | Q9CD30 | Purine NTP-dependent helicase activity | Abnormality of the outer ear | Autosomal recessive disease | Negative |
| 40 | Q9CD26 | Hydrolase activity, acting on carbon-nitrogen (but not peptide) | N/A | N/A | N/A |

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|---|---|---|---|---|---|
| | | bonds, in linear amides | | | |
| 41 | Q9CD25 | Drug binding | N/A | N/A | N/A |
| 42 | Q9CD22 | Thiolester hydrolase activity | N/A | N/A | |
| 43 | Q9CD03 | Carboxylic ester hydrolase activity | Abnormality of lipid metabolism | Meningioma | Positive |
| 44 | Q7APS9 | Acetyltransferase activity | | N/A | N/A |
| 45 | Q7APS8 | Alcohol binding | N/A | N/A | N/A |
| 46 | Q9CCZ2 | Hydrolase activity, hydrolyzing O-glycosyl compounds | N/A | N/A | N/A |
| 47 | Q7APS1 | Cysteine-type peptidase activity | N/A | Bullous skin disease | Negative |
| 48 | Q7APS0 | Carbamoyl-phosphate synthase (glutamine-hydrolyzing) activity | Hyperammonemia | N/A | N/A |
| 49 | Q9CCY3 | S-adenosylmethionine-dependent methyltransferase activity | N/A | N/A | N/A |
| 50 | Q7APR7 | Magnesium ion binding | N/A | Motor neuron disease | Positive |
| 51 | Q7APR5 | Purine NTP-dependent helicase activity | N/A | N/A | N/A |
| 52 | Q49736 | Hydrolase activity, hydrolyzing O-glycosyl compounds | Abnormality of the abdominal organs | N/A | N/A |
| 53 | Q49929 | Transferase activity, transferring hexosyl groups | N/A | Inherited metabolic disorder | Positive |
| 54 | P49774 | Adenylyltransferase activity | N/A | N/A | N/A |
| 55 | O33060 | S-adenosylmethionine-dependent methyltransferase activity | N/A | N/A | N/A |
| 56 | Q49646 | Ligand-gated channel activity | Abnormality of nervous system physiology | Temporal lobe epilepsy | Negative |
| 57 | O69492 | N-methyltransferase activity | Abnormality of the philtrum | N/A | N/A |
| 58 | Q49721 | Oxidoreductase activity, acting on NAD(P)H | N/A | N/A | N/A |
| 59 | O69462 | Oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor | N/A | N/A | N/A |
| 60 | O32912 | Oxidoreductase activity, acting on NAD(P)H | Abnormality of skeletal physiology | N/A | N/A |
| 61 | Q7APY1 | Hydrolase activity, hydrolyzing O-glycosyl compounds | N/A | N/A | N/A |
| 62 | Q9CBJ7 | Acetyltransferase activity | N/A | N/A | N/A |
| 63 | Q9CBR4 | Hydrolase activity, hydrolyzing O-glycosyl compounds | N/A | N/A | N/A |
| 64 | Q9CBK6 | Purine ribonucleoside binding | Neoplasm by anatomical site | Parasitic helminthiasis infectious disease | Positive |
| 65 | Q9CBP6 | Phosphoric diester hydrolase activity | Abnormality of circulating hormone level | N/A | N/A |
| 66 | Q9CBB6 | Isomerase activity | N/A | N/A | N/A |
| 67 | Q9CBI8 | Oxidoreductase activity | N/A | N/A | N/A |
| 68 | Q9CBP4 | Phosphoric diester hydrolase activity | N/A | N/A | N/A |
| 69 | Q9CBE8 | Opsonin binding | Decreased body weight | Autoimmune disease of skin and connective tissue | Negative |
| 70 | Q9CBP5 | Hydro-lyase activity | N/A | N/A | N/A |
| 71 | Q9CBF3 | Hydrolase activity, hydrolyzing O-glycosyl compounds | Abnormal form of the vertebral bodies | Lipid storage disease | Negative |
| 72 | Q9CBH1 | Alcohol binding | N/A | N/A | N/A |
| 73 | Q9CBR7 | Monooxygenase activity | N/A | N/A | N/A |

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|---|---|---|---|---|---|
| 74 | Q7APZ3 | Phosphatase binding | Abnormality of the lip | Autosomal dominant disease | Positive |
| 75 | Q7APZ4 | Aminoacyl-tRNA ligase activity | N/A | Benign neoplasm | Negative |
| 76 | Q49942 | N-methyltransferase activity | Abnormality of the philtrum | N/A | N/A |
| 77 | Q9CBS5 | N-methyltransferase activity | Abnormality of the philtrum | N/A | N/A |
| 78 | Q49618 | Monocarboxylic acid binding | Hypoglycemia | Primary biliary cirrhosis | Negative |
| 79 | Q7AQP5 | Phosphatase binding | Abnormality of the lip | Autosomal dominant disease | Positive |
| 80 | Q9CDE4 | Phosphatase binding | Abnormality of the pulmonary artery | Autosomal dominant disease | Positive |
| 81 | Q9CDD8 | Guanyl nucleotide binding | N/A | N/A | N/A |
| 82 | Q9CDD7 | Purine NTP-dependent helicase activity | Abnormality of the outer ear | N/A | N/A |
| 83 | Q9CDB9 | Magnesium ion binding | N/A | N/A | N/A |
| 84 | Q9CDB7 | Transferase activity, transferring hexosyl groups | Joint laxity | N/A | N/A |
| 85 | Q9CDB3 | Carboxylic ester hydrolase activity | Abnormality of lipid metabolism | Meningioma | Negative |
| 86 | Q9CD97 | N-acyltransferase activity | Behavioral abnormality | N/A | N/A |
| 87 | Q9CD92 | Monocarboxylic acid binding | N/A | N/A | N/A |
| 88 | Q9CD90 | N-methyltransferase activity | Abnormality of the philtrum | N/A | N/A |
| 89 | Q9CD74 | Intramolecular transferase activity | N/A | N/A | N/A |
| 90 | Q9CD71 | Endopeptidase activity | N/A | N/A | N/A |
| 91 | Q7AQM9 | Intramolecular oxidoreductase activity | N/A | N/A | N/A |
| 92 | Q9CD64 | N-acyltransferase activity | Abnormality of vision | N/A | N/A |
| 93 | Q9CD62 | Oxidoreductase activity, acting on the CH-NH2 group of donors | N/A | N/A | N/A |
| 94 | Q7AQM2 | DNA-dependent ATPase activity | Paralysis due to lesions of the principle motor tracts | N/A | N/A |
| 95 | Q7AQL2 | Oxidoreductase activity, acting on the CH-NH group of donors | N/A | N/A | N/A |
| 96 | Q9CD54 | Carboxy-lyase activity | N/A | N/A | N/A |
| 97 | Q9CD53 | Transferase activity, transferring hexosyl groups | N/A | N/A | N/A |
| 98 | Q7AQL0 | Unfolded protein binding | Abnormality of cranial sutures | N/A | N/A |
| 99 | Q7AQK7 | Monooxygenase activity | N/A | N/A | N/A |
| 100 | Q7AQK6 | Cysteine-type peptidase activity | N/A | N/A | N/A |
| 101 | Q7AQK5 | Thiolester hydrolase activity | N/A | N/A | N/A |
| 102 | Q7AQK0 | Catalytic activity | N/A | N/A | N/A |
| 103 | Q9CCV6 | Carboxylic ester hydrolase activity | Abnormality of lipid metabolism | Meningioma | Negative |
| 104 | Q9CCV0 | N-methyltransferase activity | Abnormality of the philtrum | N/A | N/A |
| 105 | Q9CCU2 | Monooxygenase activity | Puberty and gonadal disorders | Gonadal disease | Negative |
| 106 | Q7AQJ1 | Magnesium ion binding | N/A | Neurodegenerative disease | Positive |
| 107 | Q9CCU0 | Adenylyltransferase activity | N/A | N/A | N/A |
| 108 | Q9CCT2 | Cysteine-type peptidase activity | N/A | Autoimmune disease of skin and | Negative |

| | | | | | |
|---|---|---|---|---|---|
| | | | | connective tissue | |
| 109 | Q9CCT1 | DNA-dependent ATPase activity | Paralysis due to lesions of the principle motor tracts | N/A | N/A |
| 110 | Q7AQH4 | Metal cluster binding | N/A | N/A | N/A |
| 111 | Q7AQH3 | Metal cluster binding | N/A | N/A | N/A |
| 112 | Q9CCM8 | Purine ribonucleoside binding | Neoplasm by anatomical site | Parasitic helminthiasis infectious disease | Positive |
| 113 | Q9CCL6 | Catalytic activity | N/A | N/A | N/A |
| 114 | Q9CCK5 | Magnesium ion binding | N/A | Neurodegenerative disease | Negative |
| 115 | Q9CCJ9 | Metallopeptidase activity | Ectopia lentis | Astrocytoma | |
| 116 | Q9CCI7 | Macromolecular complex | N/A | N/A | N/A |
| 117 | Q9CCI6 | Monovalent inorganic cation transport | N/A | N/A | N/A |
| 118 | Q9CCI4 | GTPase activity | Abnormality of the hair | N/A | N/A |
| 119 | Q9CCI1 | Guanyl nucleotide binding | Abnormality of the cerebellar vermis | Autosomal recessive disease | Negative |
| 120 | Q9CCI0 | Aminoacyl-tRNA ligase activity | N/A | N/A | N/A |
| 121 | Q9CCG9 | Metallopeptidase activity | Ectopia lentis | Aortic disease | Negative |
| 122 | Q9CCG0 | Structural molecule activity | N/A | N/A | N/A |
| 123 | Q7AQF1 | Oxidoreductase activity, acting on the CH-CH group of donors | Abnormality of cell physiology | N/A | N/A |
| 124 | Q9CCF5 | Metal cluster binding | N/A | N/A | N/A |
| 125 | Q7AQE0 | Alcohol binding | N/A | N/A | N/A |
| 126 | Q7AQC8 | N-acyltransferase activity | Abnormality of nervous system physiology | N/A | N/A |
| 127 | Q9CCD1 | Nucleic acid binding transcription factor activity | Acute leukemia | Endocrine system disease | Negative |
| 128 | Q9CCC2 | P-P-bond-hydrolysis-driven transmembrane transporter activity | N/A | N/A | N/A |
| 129 | Q7AQB4 | Cellular macromolecular complex assembly | N/A | N/A | N/A |
| 130 | Q7AQA5 | Ion gated channel activity | Abnormality of cation homeostasis | N/A | N/A |
| 131 | Q7AQA4 | DNA polymerase activity | N/A | N/A | N/A |
| 132 | Q9CCB2 | Oxidoreductase activity | N/A | N/A | N/A |
| 133 | Q7AQ88 | External encapsulating structure | N/A | N/A | N/A |
| 134 | Q9CCA9 | Transferase activity, transferring hexosyl groups | Joint laxity | N/A | N/A |
| 135 | Q9CC95 | Guanyl nucleotide binding | N/A | N/A | N/A |
| 136 | Q9CC90 | Oxidoreductase activity | N/A | N/A | N/A |
| 137 | Q9CC84 | Ribonuclease activity | N/A | N/A | N/A |
| 138 | Q9CC83 | Guanyl nucleotide binding | N/A | N/A | N/A |
| 139 | Q7AQ90 | Isomerase activity | N/A | N/A | N/A |
| 140 | Q9CC76 | Oxidoreductase activity, acting on a sulfur group of donors | N/A | Normocytic anemia | Negative |
| 141 | Q7AQ86 | Hydrolase activity, hydrolyzing O-glycosyl compounds | Abnormal form of the vertebral bodies | Lipid storage disease | Negative |
| 142 | Q7AQ84 | Exopeptidase activity | N/A | N/A | N/A |
| 143 | Q9CC66 | Magnesium ion binding | N/A | Neurodegenerative disease | Negative |
| 144 | Q7AQ79 | Oxidoreductase activity, acting on the CH-NH2 group of donors | N/A | N/A | N/A |
| 145 | Q9CC45 | Ion binding | N/A | N/A | N/A |
| 146 | Q9CC41 | Intramolecular transferase activity | N/A | N/A | N/A |

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|---|---|---|---|---|---|
| 147 | Q9CC38 | Cellular macromolecular complex assembly | N/A | N/A | N/A |
| 148 | Q7AQ72 | Nuclease activity | Microcephaly | Hematopoietic system disease | Negative |
| 149 | Q7AQ71 | N-methyltransferase activity | Abnormality of the philtrum | N/A | N/A |
| 150 | Q9CC33 | Lipoprotein metabolic process | N/A | N/A | N/A |
| 151 | Q7AQ59 | Transcription regulatory region DNA binding | N/A | N/A | N/A |
| 152 | Q9CC26 | RNA binding | Vomiting | N/A | N/A |
| 153 | Q9CC25 | Thiolester hydrolase activity | N/A | N/A | N/A |
| 154 | Q9CC18 | Lyase activity | N/A | N/A | N/A |
| 155 | Q9CC07 | Intramolecular oxidoreductase activity | N/A | Adenoma | Negative |
| 156 | Q7AQ55 | Acetyltransferase activity | N/A | Lipid storage disease | Negative |
| 157 | Q9CC02 | Catalytic activity | N/A | | N/A |
| 158 | Q9CBY0 | Oxidoreductase activity, acting on a sulfur group of donors | N/A | Normocytic anemia | Negative |
| 159 | Q9CBW7 | Oxidoreductase activity, acting on the CH-NH2 group of donors | N/A | N/A | N/A |
| 160 | Q9CBW5 | Monooxygenase activity | N/A | N/A | N/A |
| 161 | Q9CBV8 | Monooxygenase activity | N/A | Hypertension | Negative |
| 162 | Q9CBV5 | DNA-dependent ATPase activity | Paralysis due to lesions of the principle motor tracts | Autosomal recessive disease | Positive |
| 163 | Q7AQ45 | Acetyltransferase activity | N/A | N/A | N/A |
| 164 | Q7AQ44 | Ribonuclease activity | N/A | N/A | N/A |
| 165 | Q7AQ41 | Oxidoreductase activity | N/A | N/A | N/A |
| 166 | Q9CBV0 | Sulfur compound binding | Abnormal facial shape | Inherited metabolic disorder | Negative |
| 167 | Q7AQ37 | DNA polymerase activity | N/A | N/A | N/A |
| 168 | Q9CB84 | Ribonuclease activity | N/A | N/A | N/A |
| 169 | Q9CB82 | S-adenosylmethionine-dependent methyltransferase activity | N/A | N/A | N/A |
| 170 | Q7APW5 | Carboxyl- or carbamoyltransferase activity | N/A | N/A | N/A |
| 171 | Q7APW4 | Hormone binding | N/A | N/A | N/A |
| 172 | Q7APW3 | Flavin adenine dinucleotide binding | N/A | N/A | N/A |
| 173 | Q9CB74 | N-methyltransferase activity | Abnormality of the philtrum | N/A | N/A |
| 174 | Q9CB73 | N-acyltransferase activity | Behavioral abnormality | Diabetes mellitus | Negative |
| 175 | Q9CB61 | Oxidoreductase activity, acting on a sulfur group of donors | N/A | Adenoma | Negative |
| 176 | Q9CB38 | Acetyltransferase activity | N/A | N/A | N/A |
| 177 | Q9CB37 | Lipid homeostasis | N/A | N/A | N/A |

N/A* - Not available

Further, homology of 43 sequences (which had DO term) with human proteome were analyzed by NCBI BLASTP program. BLASTP program was performed against UniProt-KB database for human proteome with an e value 0.001. Hits were considered as true positive (homologs), when it had an identity of >30% and a coverage of >70%. We found that 13 sequences were homologous to human proteome, while the remaining 30 sequences with DO term did not show homology with Human proteome. These 30 sequences might be used as putative drug target for M. leprae. UniProt-KB Sequence ID for these sequences was tabulated in supplementary **Table 1**.

Essential genes in prokaryotes have a minimal genome, which play the key roles in metabolism. Database of Essential Gene (DEG) constitute a minimal genome, forming a set of functional modules, which play the important role in metabolism. DEG BLASTp report suggested that out of 177 sequences, 101 sequences had at least one prokaryotic DEG homologous sequences. These 101 sequences were found to contain 494 DEG homologous genes. These sequences might be used as putative drug target for *M. leprae* (supplementary **Table 2**).

## Supplementary:

**TABLE 2: LIST OF 101 SEQUENCES (OUT OF 177 SEQUENCES) CONTAINING 494 DEG HOMOLOGOUS GENES**

| Sl no. | Query Protein | No. of homologs in DEG | DEG AC Number |
|---|---|---|---|
| 1 | tr\|Q9CBR0\|Q9CBR0_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1720 PE=4 SV=1 | 2 | DEG10270551; DEG10250602 |
| 2 | tr\|Q9CBR1\|Q9CBR1_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1719 PE=4 SV=1 | 5 | DEG10340229; DEG10150073; DEG10110123; DEG10270550; DEG10250601 |
| 3 | tr\|Q9CBQ9\|Q9CBQ9_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1723 PE=4 SV=1 | 3 | DEG10270552; DEG10280353; DEG10250603; |
| 4 | tr\|Q9CBM5\|Q9CBM5_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1802 PE=4 SV=1 | 3 | DEG10300085; DEG10110223; DEG10300086 |
| 5 | tr\|Q7APZ6\|Q7APZ6_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML2073 PE=4 SV=1 | 2 | DEG10270344; DEG10250373 |
| 6 | tr\|Q9CBI9\|Q9CBI9_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1921 PE=4 SV=1 | 1 | DEG10270628 |
| 7 | tr\|Q7AQ25\|Q7AQ25_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1713 PE=4 SV=1 | 10 | DEG10100492; DEG10130008; DEG10200110; DEG10280490; DEG10250034; DEG10270038; DEG10150116; DEG10270548; DEG10250598; DEG10100017 |
| 8 | tr\|Q9CBC4\|Q9CBC4_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML2203 PE=3 SV=1 | 5 | DEG10240254; DEG10290088; DEG10100132; DEG10270151; DEG10250156 |
| 9 | sp\|O33089\|Y055_MYCLE Uncharacterized protein ML0055 OS=*Mycobacterium leprae* (strain TN) GN=ML0055 PE=3 SV=1 | 9 | DEG10170233; DEG10250510; DEG10250045; DEG10270338; DEG10270049; DEG10080186; DEG10210007; DEG10070009; DEG10100022 |
| 10 | sp\|Q49857\|Y378_MYCLE Uncharacterized protein ML0378 OS=*Mycobacterium leprae* (strain TN) GN=ML0378 PE=4 SV=1 | 18 | DEG10240228; DEG10320168; DEG10160084; DEG10130115; DEG10150091; DEG10230100; DEG10030387; DEG10330086; DEG10340377; DEG10010074; DEG10110106; DEG10280237; DEG10070117; DEG10200015; DEG10170288; DEG10290242; DEG10180306; DEG10190124 |
| 11 | sp\|Q49741\|Y393_MYCLE Uncharacterized protein ML0393 OS=*Mycobacterium leprae* (strain TN) GN=ML0393 PE=4 SV=1 | 2 | DEG10270355; DEG10250385 |
| 12 | sp\|Q57240\|Y396_MYCLE Uncharacterized protein ML0396/ML2692 OS=*Mycobacterium leprae* (strain TN) GN=ML0396 PE=3 SV=1 | 2 | DEG10270014; DEG10250013 |
| 13 | sp\|Q49649\|Y493_MYCLE Uncharacterized | 2 | DEG10250505; DEG10100364 |

| | | | |
|---|---|---|---|
| | protein ML0493 OS=*Mycobacterium leprae* (strain TN) GN=ML0493 PE=3 SV=1 | | |
| 14 | sp\|Q49755\|Y605_MYCLE Uncharacterized protein ML0605 OS=*Mycobacterium leprae* (strain TN) GN=ML0605 PE=4 SV=2 | 2 | DEG10250502; DEG10270473 |
| 15 | sp\|Q9CC91\|Y1105_MYCLE Uncharacterized protein ML1105 OS=*Mycobacterium leprae* (strain TN) GN=ML1105 PE=4 SV=1 | 2 | DEG10240229; DEG10200191 |
| 16 | sp\|P53426\|Y1171_MYCLE Uncharacterized protein ML1171 OS=*Mycobacterium leprae* (strain TN) GN=ML1171 PE=4 SV=1 | 1 | DEG10230292 |
| 17 | sp\|P50474\|Y1173_MYCLE Uncharacterized protein ML1173 OS=*Mycobacterium leprae* (strain TN) GN=ML1173 PE=3 SV=1 | 3 | DEG10100212; DEG10270245; DEG10250250 |
| 18 | sp\|P54882\|Y2434_MYCLE Uncharacterized protein ML2434 OS=*Mycobacterium leprae* (strain TN) GN=ML2434 PE=3 SV=2 | 4 | DEG10310035; DEG10100159; DEG10300098; DEG10130380 |
| 19 | sp\|Q9CD28\|Y2537_MYCLE Uncharacterized protein ML2537 OS=*Mycobacterium leprae* (strain TN) GN=ML2537 PE=4 SV=1 | 5 | DEG10270338; DEG10280402; DEG10250045; DEG10100022; DEG10270049 |
| 20 | sp\|O05668\|Y1370_MYCLE Uncharacterized RNA pseudouridine synthase ML1370 OS=*Mycobacterium leprae* (strain TN) GN=ML1370 PE=3 SV=1 | 8 | DEG10050444; DEG10220254; DEG10270327; DEG10100297; DEG10250360; DEG10230257; DEG10180218; DEG10340427 |
| 21 | sp\|Q9CCW4\|Y324_MYCLE Uncharacterized tRNA/rRNA methyltransferase ML0324 OS=*Mycobacterium leprae* (strain TN) GN=ML0324 PE=3 SV=2 | 4 | DEG10270623; DEG10110147; DEG10250688; DEG10100556 |
| 22 | sp\|O32965\|Y855_MYCLE Uncharacterized zinc protease ML0855 OS=*Mycobacterium leprae* (strain TN) GN=ML0855 PE=3 SV=1 | 1 | DEG10080170 |
| 23 | tr\|Q9CD30\|Q9CD30_MYCLE Putative uncharacterized protein ML2535 OS=*Mycobacterium leprae* (strain TN) GN=ML2535 PE=4 SV=1 | 7 | DEG10270333; DEG10270604; DEG10250047; DEG10130148; DEG10250365; DEG10100024; DEG10270051 |
| 24 | tr\|Q9CD26\|Q9CD26_MYCLE Putative uncharacterized protein ML2549 OS=*Mycobacterium leprae* (strain TN) GN=ML2549 PE=4 SV=1 | 1 | DEG10050635 |
| 25 | tr\|Q9CD22\|Q9CD22_MYCLE Putative uncharacterized protein ML2566 OS=*Mycobacterium leprae* (strain TN) GN=ML2566 PE=4 SV=1 | 4 | DEG10250495; DEG10270046; DEG10100406; DEG10270469 |
| 26 | tr\|Q7APS9\|Q7APS9_MYCLE Putative uncharacterized protein ML2627 OS=*Mycobacterium leprae* (strain TN) GN=ML2627 PE=4 SV=1 | 1 | DEG10270036 |
| 27 | tr\|Q7APS8\|Q7APS8_MYCLE Putative uncharacterized protein ML2629 OS=*Mycobacterium leprae* (strain TN) GN=ML2629 PE=4 SV=1 | 1 | DEG10250027 |
| 28 | tr\|Q7APS0\|Q7APS0_MYCLE Putative uncharacterized protein ML2679 OS=*Mycobacterium leprae* (strain TN) GN=ML2679 PE=4 SV=1 | 2 | DEG10250502; DEG10270473 |
| 29 | tr\|Q7APR5\|Q7APR5_MYCLE Putative uncharacterized protein ML2709 OS=*Mycobacterium leprae* (strain TN) GN=ML2709 PE=4 SV=1 | 1 | DEG10070107 |
| 30 | sp\|Q49736\|Y392_MYCLE Uncharacterized | 2 | DEG10270355; DEG10250385 |

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|---|---|---|---|
| | glycosyl hydrolase ML0392 OS=*Mycobacterium leprae* (strain TN) GN=ML0392 PE=3 SV=1 | | |
| 31 | sp\|Q49929\|Y2348_MYCLE Uncharacterized glycosyl transferase ML2348 OS=*Mycobacterium leprae* (strain TN) GN=ML2348 PE=3 SV=1 | 2 | DEG10350435; DEG10350472 |
| 32 | sp\|P49774\|YHI1_MYCLE Uncharacterized HIT-like protein ML2237 OS=*Mycobacterium leprae* (strain TN) GN=ML2237 PE=4 SV=2 | 1 | DEG10140005 |
| 33 | sp\|O69492\|Y2584_MYCLE Uncharacterized methyl transferase ML2584 OS=*Mycobacterium leprae* (strain TN) GN=ML2584 PE=3 SV=1 | 3 | DEG10100017; DEG10270038; DEG10250034 |
| 34 | sp\|Q49721\|Y388_MYCLE Uncharacterized oxido-reductase ML0388 OS=*Mycobacterium leprae* (strain TN) GN=ML0388 PE=3 SV=1 | 14 | DEG10240247; DEG10150086; DEG10070111; DEG10100536; DEG10020023; DEG10270599; DEG10270598; DEG10010005; DEG10280044; DEG10250668; DEG10250667; DEG10130475; DEG10310139; DEG10350247 |
| 35 | sp\|O69462\|Y1669_MYCLE Uncharacterized oxido-reductase ML1669 OS=*Mycobacterium leprae* (strain TN) GN=ML1669 PE=3 SV=1 | 3 | DEG10100474; DEG10270532; DEG10250576 |
| 36 | sp\|O32912\|Y2066_MYCLE Uncharacterized oxidoreductase ML2066 OS=*Mycobacterium leprae* (strain TN) GN=ML2066 PE=3 SV=1 | 16 | DEG10240247; DEG10150086; DEG10220288; DEG10130475; DEG10020023; DEG10270599; DEG10310139; DEG10080148; DEG10250667; DEG10280044; DEG10250668; DEG10010005; DEG10270598; DEG10070111; DEG10100536; DEG10350247 |
| 37 | tr\|Q9CBJ7\|Q9CBJ7_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1909 PE=4 SV=1 | 3 | DEG10100087; DEG10270046; DEG10250119 |
| 38 | tr\|Q9CBR4\|Q9CBR4_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1714 PE=4 SV=1 | 3 | DEG10250599; DEG10270549; DEG10100493 |
| 39 | tr\|Q9CBK6\|Q9CBK6_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1898 PE=4 SV=1 | 12 | DEG10160246; DEG10150313; DEG10180557; DEG10270113; DEG10290356; DEG10350038; DEG10120114; DEG10190266; DEG10250126; DEG10320318; DEG10240040; DEG10330249 |
| 40 | tr\|Q9CBP6\|Q9CBP6_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1750 PE=4 SV=1 | 4 | DEG10350500; DEG10350034; DEG10130392; DEG10270248 |
| 41 | tr\|Q9CBP4\|Q9CBP4_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1752 PE=4 SV=1 | 3 | DEG10350034; DEG10130392; DEG10270248 |
| 42 | tr\|Q9CBE8\|Q9CBE8_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML2070 PE=4 SV=1 | 1 | DEG10250375 |
| 43 | tr\|Q9CBP5\|Q9CBP5_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1751 PE=4 SV=1 | 11 | DEG10050052; DEG10270418; DEG10130285; DEG10220078; DEG10050529; DEG10280532; DEG10340076; DEG10100369; DEG10250255; DEG10270249; DEG10230223 |
| 44 | tr\|Q7APZ3\|Q7APZ3_MYCLE Uncharacterized | 3 | DEG10250371; DEG10250009; |

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|---|---|---|---|
| | protein OS=*Mycobacterium leprae* (strain TN) GN=ML2076 PE=4 SV=1 | | DEG10270010 |
| 45 | tr\|Q7APZ4\|Q7APZ4_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML2075 PE=4 SV=1 | 3 | DEG10100305; DEG10250372; DEG10270343 |
| 46 | tr\|Q9CBS5\|Q9CBS5_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=ML1664 PE=4 SV=1 | 4 | DEG10280275; DEG10290385; DEG10180524; DEG10050260 |
| 47 | tr\|Q49618\|Q49618_MYCLE Uncharacterized protein OS=*Mycobacterium leprae* (strain TN) GN=papA3 PE=4 SV=1 | 2 | DEG10100171; DEG10270671 |
| 48 | tr\|Q7AQP5\|Q7AQP5_MYCLE Putative uncharacterized protein ML0021 OS=*Mycobacterium leprae* (strain TN) GN=ML0021 PE=4 SV=1 | 1 | DEG10250371 |
| 49 | tr\|Q9CDE4\|Q9CDE4_MYCLE Putative uncharacterized protein ML0022 OS=*Mycobacterium leprae* (strain TN) GN=ML0022 PE=4 SV=1 | 3 | DEG10250371; DEG10250009; DEG10270010 |
| 50 | tr\|Q9CDD8\|Q9CDD8_MYCLE Putative uncharacterized protein ML0048 OS=*Mycobacterium leprae* (strain TN) GN=ML0048 PE=4 SV=1 | 1 | DEG10250761 |
| 51 | tr\|Q9CDD7\|Q9CDD7_MYCLE Putative uncharacterized protein ML0052 OS=*Mycobacterium leprae* (strain TN) GN=ML0052 PE=4 SV=1 | 6 | DEG10270333; DEG10270604; DEG10250047; DEG10250365; DEG10100024; DEG10270051 |
| 52 | tr\|Q9CDB9\|Q9CDB9_MYCLE Putative uncharacterized protein ML0089 OS=*Mycobacterium leprae* (strain TN) GN=ML0089 PE=4 SV=1 | 2 | DEG10180129; DEG10140113 |
| 53 | tr\|Q9CDB7\|Q9CDB7_MYCLE Putative uncharacterized protein ML0093 OS=*Mycobacterium leprae* (strain TN) GN=ML0093 PE=4 SV=1 | 4 | DEG10250749; DEG10320079; DEG10270668; DEG10100604 |
| 54 | tr\|Q9CDB3\|Q9CDB3_MYCLE Putative uncharacterized protein ML0099 OS=*Mycobacterium leprae* (strain TN) GN=ML0099 PE=4 SV=1 | 2 | DEG10100601; DEG10250745 |
| 55 | tr\|Q9CD97\|Q9CD97_MYCLE Putative uncharacterized protein ML0117 OS=*Mycobacterium leprae* (strain TN) GN=ML0117 PE=3 SV=1 | 16 | DEG10340054; DEG10100590; DEG10350470; DEG10110161; DEG10350293; DEG10200232; DEG10270654; DEG10010234; DEG10230199; DEG10250730; DEG10020079; DEG10170086; DEG10120177; DEG10220155; DEG10250285; DEG10100244 |
| 56 | tr\|Q9CD92\|Q9CD92_MYCLE Putative uncharacterized protein ML0124 OS=*Mycobacterium leprae* (strain TN) GN=ML0124 PE=4 SV=1 | 1 | DEG10250027 |
| 57 | tr\|Q9CD71\|Q9CD71_MYCLE Putative uncharacterized protein ML0154 OS=*Mycobacterium leprae* (strain TN) GN=ML0154 PE=4 SV=1 | 15 | DEG10350112; DEG10050255; DEG10290358; DEG10260033; DEG10300077; DEG10340373; DEG10300117; DEG10230098; DEG10300092; DEG10340112; DEG10220206; DEG10230271; DEG10310161; DEG10200294; DEG10300022 |
| 58 | tr\|Q7AQM9\|Q7AQM9_MYCLE Putative | 1 | DEG10280264 |

| | | | |
|---|---|---|---|
| | uncharacterized protein ML0181 OS=*Mycobacterium leprae* (strain TN) GN=ML0181 PE=4 SV=1 | | |
| 59 | tr\|Q9CD64\|Q9CD64_MYCLE Putative uncharacterized protein ML0187 OS=*Mycobacterium leprae* (strain TN) GN=ML0187 PE=4 SV=1 | 1 | DEG10300113 |
| 60 | tr\|Q9CD62\|Q9CD62_MYCLE Putative uncharacterized protein ML0190 OS=*Mycobacterium leprae* (strain TN) GN=ML0190 PE=4 SV=1 | 1 | DEG10030762 |
| 61 | tr\|Q7AQM2\|Q7AQM2_MYCLE Putative uncharacterized protein ML0202 OS=*Mycobacterium leprae* (strain TN) GN=ML0202 PE=4 SV=1 | 46 | DEG10170021; DEG10160163; DEG10170024; DEG10030223; DEG10220190; DEG10180088; DEG10330116; DEG10050150; DEG10060340; DEG10120142; DEG10280012; DEG10250711; DEG10340444; DEG10240273; DEG10320058; DEG10140019; DEG10270651; DEG10210104; DEG10230247; DEG10190054; DEG10020026; DEG10320116; DEG10070050; DEG10190092; DEG10330166; DEG10230084; DEG10130241; DEG10290186; DEG10250726; DEG10180182; DEG10160114; DEG10010007; DEG10130274; DEG10120034; DEG10350111; DEG10030388; DEG10200228; DEG10200037; DEG10270640; DEG10290244; DEG10070046; DEG10240256; DEG10280073; DEG10010009; DEG10210151; DEG10100587; |
| 62 | tr\|Q7AQL2\|Q7AQL2_MYCLE Putative uncharacterized protein ML0229 OS=*Mycobacterium leprae* (strain TN) GN=ML0229 PE=4 SV=1 | 2 | DEG10250700; DEG10270633 |
| 63 | tr\|Q9CD54\|Q9CD54_MYCLE Putative uncharacterized protein ML0239 OS=*Mycobacterium leprae* (strain TN) GN=ML0239 PE=4 SV=1 | 4 | DEG10180608; DEG10050036; DEG10020032; DEG10120173 |
| 64 | tr\|Q7AQL0\|Q7AQL0_MYCLE Putative uncharacterized protein ML0258 OS=*Mycobacterium leprae* (strain TN) GN=ML0258 PE=4 SV=1 | 4 | DEG10310035; DEG10100159; DEG10300098; DEG10130380 |
| 65 | tr\|Q7AQK0\|Q7AQK0_MYCLE Putative uncharacterized protein ML0298 OS=*Mycobacterium leprae* (strain TN) GN=ML0298 PE=4 SV=1 | 1 | DEG10100052 |
| 66 | tr\|Q9CCU0\|Q9CCU0_MYCLE Putative uncharacterized protein ML0455 OS=*Mycobacterium leprae* (strain TN) GN=ML0455 PE=4 SV=1 | 3 | DEG10100420; DEG10140005; DEG10060106 |
| 67 | tr\|Q9CCT1\|Q9CCT1_MYCLE Putative uncharacterized protein ML0510 OS=*Mycobacterium leprae* (strain TN) GN=ML0510 PE=4 SV=1 | 27 | DEG10170233; DEG10160083; DEG10160163; DEG10030223; DEG10220190; DEG10220302; DEG10240273; DEG10350353; DEG10320058; DEG10070046; DEG10230084; DEG10330085; |

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|---|---|---|---|
| | | | DEG10210007; DEG10190054; DEG10110113; DEG10330166; DEG10130241; DEG10290186; DEG10340021; DEG10180088; DEG10300027; DEG10120034; DEG10350111; DEG10280012; DEG10140019; DEG10070009; DEG10250510; |
| 68 | tr\|Q7AQH4\|Q7AQH4_MYCLE Putative uncharacterized protein ML0597 OS=*Mycobacterium leprae* (strain TN) GN=ML0597 PE=4 SV=1 | 7 | DEG10010233; DEG10140060; DEG10030159; DEG10240213; DEG10170087; DEG10100245; DEG10250286 |
| 69 | tr\|Q7AQH3\|Q7AQH3_MYCLE Putative uncharacterized protein ML0598 OS=*Mycobacterium leprae* (strain TN) GN=ML0598 PE=4 SV=1 | 2 | DEG10280315; DEG10100246 |
| 70 | tr\|Q9CCM8\|Q9CCM8_MYCLE Putative uncharacterized protein ML0640 OS=*Mycobacterium leprae* (strain TN) GN=ML0640 PE=4 SV=1 | 12 | DEG10160246; DEG10150313; DEG10180557; DEG10270113; DEG10290356; DEG10350038; DEG10120114; DEG10190266; DEG10250126; DEG10320318; DEG10240040; DEG10330249 |
| 71 | tr\|Q9CCI4\|Q9CCI4_MYCLE Putative uncharacterized protein ML0791 OS=*Mycobacterium leprae* (strain TN) GN=ML0791 PE=3 SV=1 | 10 | DEG10230127; DEG10160339; DEG10340097; DEG10010188; DEG10330344; DEG10170218; DEG10320344; DEG10010114; DEG10170138; DEG10290073 |
| 72 | tr\|Q9CCI1\|Q9CCI1_MYCLE Putative uncharacterized protein ML0798 OS=*Mycobacterium leprae* (strain TN) GN=ML0798 PE=4 SV=1 | 5 | DEG10270338; DEG10250045; DEG10250761; DEG10270049; DEG10100022 |
| 73 | tr\|Q9CCF5\|Q9CCF5_MYCLE Putative uncharacterized protein ML0871 OS=*Mycobacterium leprae* (strain TN) GN=ML0871 PE=4 SV=1 | 18 | DEG10030160; DEG10240146; DEG10280444; DEG10160030; DEG10150079; DEG10290205; DEG10190025; DEG10330031; DEG10130209; DEG10130003; DEG10120153; DEG10030128; DEG10120178; DEG10240214; DEG10150028; DEG10320029; DEG10180280; DEG10290123 |
| 74 | tr\|Q7AQA4\|Q7AQA4_MYCLE Putative uncharacterized protein ML1040 OS=*Mycobacterium leprae* (strain TN) GN=ML1040 PE=4 SV=1 | 3 | DEG10280310; DEG10200443; DEG10200221 |
| 75 | tr\|Q9CCB2\|Q9CCB2_MYCLE Putative uncharacterized protein ML1045 OS=*Mycobacterium leprae* (strain TN) GN=ML1045 PE=4 SV=1 | 2 | DEG10250519; DEG10270483 |
| 76 | tr\|Q7AQ88\|Q7AQ88_MYCLE Putative uncharacterized protein ML1053 OS=*Mycobacterium leprae* (strain TN) GN=ML1053 PE=4 SV=1 | 11 | DEG10270156; DEG10270610; DEG10270611; DEG10270134; DEG10100169; DEG10270048; DEG10270346; DEG10270026; DEG10250685; DEG10250684; DEG10270627 |
| 77 | tr\|Q9CCA9\|Q9CCA9_MYCLE Putative uncharacterized protein ML1064 OS=*Mycobacterium leprae* (strain TN) GN=ML1064 PE=4 SV=1 | 3 | DEG10100179; DEG10270214; DEG10250221 |
| 78 | tr\|Q9CC95\|Q9CC95_MYCLE Putative uncharacterized protein ML1098 | 1 | DEG10270218 |

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|---|---|---|---|
| | OS=*Mycobacterium leprae* (strain TN) GN=ML1098 PE=4 SV=1 | | |
| 79 | tr\|Q9CC83\|Q9CC83_MYCLE Putative uncharacterized protein ML1120 OS=*Mycobacterium leprae* (strain TN) GN=ML1120 PE=4 SV=1 | 1 | DEG10100187 |
| 80 | tr\|Q7AQ90\|Q7AQ90_MYCLE Putative uncharacterized protein ML1157 OS=*Mycobacterium leprae* (strain TN) GN=ML1157 PE=4 SV=1 | 1 | DEG10220085 |
| 81 | tr\|Q9CC76\|Q9CC76_MYCLE Putative uncharacterized protein ML1159 OS=*Mycobacterium leprae* (strain TN) GN=ML1159 PE=4 SV=1 | 2 | DEG10110205; DEG10030730 |
| 82 | tr\|Q7AQ84\|Q7AQ84_MYCLE Putative uncharacterized protein ML1193 OS=*Mycobacterium leprae* (strain TN) GN=ML1193 PE=4 SV=1 | 12 | DEG10330064; DEG10290238; DEG10180376; DEG10350264; DEG10200039; DEG10160063; DEG10320196; DEG10190141; DEG10240231; DEG10130124; DEG10110140; DEG10030414 |
| 83 | tr\|Q9CC66\|Q9CC66_MYCLE Putative uncharacterized protein ML1224 OS=*Mycobacterium leprae* (strain TN) GN=ML1224 PE=4 SV=1 | 1 | DEG10030576 |
| 84 | tr\|Q7AQ79\|Q7AQ79_MYCLE Putative uncharacterized protein ML1249 OS=*Mycobacterium leprae* (strain TN) GN=ML1249 PE=4 SV=1 | 2 | DEG10270456; DEG10250486 |
| 85 | tr\|Q9CC45\|Q9CC45_MYCLE Putative uncharacterized protein ML1289 OS=*Mycobacterium leprae* (strain TN) GN=ML1289 PE=4 SV=1 | 1 | DEG10080034 |
| 86 | tr\|Q9CC41\|Q9CC41_MYCLE Putative uncharacterized protein ML1298 OS=*Mycobacterium leprae* (strain TN) GN=ML1298 PE=4 SV=1 | 5 | DEG10250442; DEG10270095; DEG10250104; DEG10270403; DEG10100068 |
| 87 | tr\|Q7AQ72\|Q7AQ72_MYCLE Putative uncharacterized protein ML1312 OS=*Mycobacterium leprae* (strain TN) GN=ML1312 PE=4 SV=1 | 1 | DEG10100513 |
| 88 | tr\|Q9CC33\|Q9CC33_MYCLE Putative uncharacterized protein ML1347 OS=*Mycobacterium leprae* (strain TN) GN=ML1347 PE=4 SV=1 | 1 | DEG10150126 |
| 89 | tr\|Q7AQ59\|Q7AQ59_MYCLE Putative uncharacterized protein ML1369 OS=*Mycobacterium leprae* (strain TN) GN=ML1369 PE=3 SV=1 | 2 | DEG10010167; DEG10140034 |
| 90 | tr\|Q9CC26\|Q9CC26_MYCLE Putative uncharacterized protein ML1390 OS=*Mycobacterium leprae* (strain TN) GN=ML1390 PE=4 SV=1 | 1 | DEG10250341 |
| 91 | tr\|Q9CC25\|Q9CC25_MYCLE Putative uncharacterized protein ML1391 OS=*Mycobacterium leprae* (strain TN) GN=ML1391 PE=4 SV=1 | 2 | DEG10250505; DEG10100364 |
| 92 | tr\|Q7AQ55\|Q7AQ55_MYCLE Putative uncharacterized protein ML1423 OS=*Mycobacterium leprae* (strain TN) GN=ML1423 PE=4 SV=1 | 2 | DEG10220387; DEG10270360 |

| | | | |
|---|---|---|---|
| 93 | tr\|Q9CBW5\|Q9CBW5_MYCLE Putative uncharacterized protein ML1512 OS=*Mycobacterium leprae* (strain TN) GN=ML1512 PE=4 SV=1 | 12 | DEG10060343; DEG10070034; DEG10170169; DEG10060111; DEG10020093; DEG10170110; DEG10010095; DEG10210042; DEG10020140; DEG10140275; DEG10140276; DEG10070004 |
| 94 | tr\|Q9CBV5\|Q9CBV5_MYCLE Putative uncharacterized protein ML1536 OS=*Mycobacterium leprae* (strain TN) GN=ML1536 PE=4 SV=1 | 5 | DEG10280402; DEG10250045; DEG10270338; DEG10270049; DEG10100022 |
| 95 | tr\|Q7AQ45\|Q7AQ45_MYCLE Putative uncharacterized protein ML1547 OS=*Mycobacterium leprae* (strain TN) GN=ML1547 PE=4 SV=1 | 2 | DEG10250542; DEG10150227 |
| 96 | tr\|Q7AQ37\|Q7AQ37_MYCLE Putative uncharacterized protein ML1637 OS=*Mycobacterium leprae* (strain TN) GN=ML1637 PE=4 SV=1 | 6 | DEG10270095; DEG10100068; DEG10250104; DEG10270403; DEG10250442; DEG10280212 |
| 97 | tr\|Q7APW5\|Q7APW5_MYCLE Putative uncharacterized protein ML2327 OS=*Mycobacterium leprae* (strain TN) GN=ML2327 PE=4 SV=1 | 6 | DEG10070084; DEG10270650; DEG10250723; DEG10100586; DEG10210082; DEG10170271; |
| 98 | tr\|Q7APW3\|Q7APW3_MYCLE Putative uncharacterized protein ML2333 OS=*Mycobacterium leprae* (strain TN) GN=ML2333 PE=4 SV=1 | 4 | DEG10250724; DEG10250736; DEG10100593; DEG10270657 |
| 99 | tr\|Q9CB74\|Q9CB74_MYCLE Putative uncharacterized protein ML2334 OS=*Mycobacterium leprae* (strain TN) GN=ML2334 PE=4 SV=1 | 2 | DEG10250725; DEG10250125 |
| 100 | tr\|Q9CB73\|Q9CB73_MYCLE Putative uncharacterized protein ML2336 OS=*Mycobacterium leprae* (strain TN) GN=ML2336 PE=4 SV=1 | 3 | DEG10250727; DEG10270652; DEG10100588 |
| 101 | tr\|Q9CB61\|Q9CB61_MYCLE Putative uncharacterized protein ML2412 OS=*Mycobacterium leprae* (strain TN) GN=ML2412 PE=4 SV=1 | 4 | DEG10250717; DEG10010166; DEG10100069; DEG10250105; |

Total protein-coding genes in your sequence: 177 genes
In our sequence, the no. of genes having homologs with DEG: 101 genes
In DEG, the no. of genes having homologs with our sequence: 494 genes

KASS was used to predict Pathway associations for the 177 sequences that have GO term and had at least one functional annotated conserved domain. KASS was performed using the BBH method (Best bidirectional Hit) from which we found that 50 sequences had KEGG orthology hits. Out of these 50 hits, 15 sequences were found to be associated with 39 KEGG pathways, which are shown in supplementary **Table 3**. KASS report provides important information about the protein (enzyme) associated in metabolic pathway.

## Supplementary:

**TABLE 3: LIST OF 50 SEQUENCES HAVING KEGG ORTHOLOGY HITS OBTAINED THROUGH KASS**

| Sl no. | Query ID | KEGG Orthology ID | Pathway | KEGG Enzyme Nomenclature |
|---|---|---|---|---|
| 1 | Q9CCZ0 | K07095 | No Hits | No Hits |
| 2 | Q9CBR1 | K00680 | ko01120 Microbial metabolism in diverse environments<br>ko00350 Tyrosine metabolism<br>ko00903 Limonene and pinene degradation<br>ko00362 Benzoate degradation | EC: 2.3.1.- |

| | | | | |
|---|---|---|---|---|
| | | | ko00627 Aminobenzoate degradation<br>ko00642 Ethylbenzene degradation | |
| 3 | Q9CBR8 | K03574 | No Hits | No Hits |
| 4 | Q9CBI9 | K01567 | No Hits | No Hits |
| 5 | Q9CBC4 | K06980 | No Hits | No Hits |
| 6 | Q49741 | K01567 | No Hits | No Hits |
| 7 | Q57240 | K01858 | ko01100 Metabolic pathways<br>ko01110 Biosynthesis of secondary metabolites<br>ko00562 Inositol phosphate metabolism<br>ko00521 Streptomycin biosynthesis | Myo-inositol-1-phosphate synthase [EC:5.5.1.4] |
| 8 | Q9CC85 | K08296 | No Hits | No Hits |
| 9 | P53425 | K01567 | No Hits | No Hits |
| 10 | P54882 | K01524 | ko00230 Purine metabolism | ppx-gppA; exopolyphosphatase / guanosine-5'-triphosphate,3'-diphosphate pyrophosphatase [EC:3.6.1.11 3.6.1.40] |
| 11 | O05668 | K06178 | No Hits | No Hits |
| 12 | Q9CCW4 | K03218 | No Hits | No Hits |
| 13 | O32965 | K01417 | No Hits | No Hits |
| 14 | Q9CD03 | K01175 | No Hits | No Hits |
| 15 | Q7APR5 | K06346 | No Hits | No Hits |
| 16 | Q49646 | K02035 | No Hits | No Hits |
| 17 | Q49721 | K00088 | ko01100 Metabolic pathways<br>ko01110 Biosynthesis of secondary metabolites<br>ko00230 Purine metabolism<br>ko00983 Drug metabolism - other enzymes | guaB; IMP dehydrogenase [EC:1.1.1.205] |
| 18 | O32912 | K00088 | ko01100 Metabolic pathways<br>ko01110 Biosynthesis of secondary metabolites<br>ko00230 Purine metabolism<br>ko00983 Drug metabolism - other enzymes | guaB; IMP dehydrogenase [EC:1.1.1.205] |
| 19 | Q9CBR4 | K16149 | ko00500 Starch and sucrose metabolism | 1,4-alpha-glucan branching enzyme [EC:2.4.1.18] |
| 20 | Q9CDB9 | K07024 | No Hits | No Hits |
| 21 | Q9CDB7 | K16650 | No Hits | No Hits |
| 22 | Q9CD74 | K04093 | ko01100 Metabolic pathways<br>ko01110 Biosynthesis of secondary metabolites<br>ko01230 Biosynthesis of amino acids<br>ko00400 Phenylalanine, tyrosine and tryptophan biosynthesis | pheA1; chorismatemutase [EC:5.4.99.5] |
| 23 | Q7AQM2 | K02341 | ko01100 Metabolic pathways<br>ko00230 Purine metabolism<br>ko00240 Pyrimidine metabolism<br>ko03030 DNA replication<br>ko03430 Mismatch repair<br>ko03440 Homologous recombination | DPO3D2; DNA polymerase III subunit delta' [EC:2.7.7.7] |
| 24 | Q9CD54 | K03424 | No Hits | No Hits |
| 25 | Q7AQL0 | K01524 | ko00230 Purine metabolism | ppx-gppA; exopolyphosphatase / guanosine-5'-triphosphate,3'-diphosphate pyrophosphatase [EC:3.6.1.11 3.6.1.40] |

| | | | | |
|---|---|---|---|---|
| 26 | Q7AQK0 | K03154 | ko04122 Sulfur relay system | thiS; sulfur carrier protein |
| 27 | Q9CCT1 | K07478 | No Hits | No Hits |
| 28 | Q7AQH4 | K04488 | No Hits | No Hits |
| 29 | Q9CCI6 | K07228 | No Hits | No Hits |
| 30 | Q9CCI4 | K06949 | No Hits | No Hits |
| 31 | Q7AQF1 | K00232 | ko01100 Metabolic pathways<br>ko01212 Fatty acid metabolism<br>ko00071 Fatty acid degradation<br>ko00592 alpha-Linolenic acid metabolism<br>ko01040 Biosynthesis of unsaturated fatty acids<br>ko04024 cAMP signaling pathway<br>ko04146 Peroxisome<br>ko03320 PPAR signaling pathway | E1.3.3.6; acyl-CoA oxidase [EC:1.3.3.6] |
| 32 | Q9CCC2 | K10533 | ko01110 Biosynthesis of secondary metabolites<br>ko00903 Limonene and pinene degradation | E3.3.2.8; limonene-1,2-epoxide hydrolase [EC:3.3.2.8] |
| 33 | Q7AQA4 | K03684 | No Hits | No Hits |
| 34 | Q9CCB2 | K09162 | No Hits | No Hits |
| 35 | Q9CCA9 | K13693 | No Hits | No Hits |
| 36 | Q9CC95 | K06860 | No Hits | No Hits |
| 37 | Q9CC76 | K05838 | No Hits | No Hits |
| 38 | Q7AQ79 | K15371 | ko01100 Metabolic pathways<br>ko00910 Nitrogen metabolism<br>ko00250 Alanine, aspartate and glutamate metabolism<br>ko00330 Arginine and proline metabolism<br>ko00430 Taurine and hypotaurine metabolism | GDH2; glutamate dehydrogenase [EC:1.4.1.2] |
| 39 | Q9CC45 | K06910 | No Hits | No Hits |
| 40 | Q7AQ72 | K07465 | No Hits | No Hits |
| 41 | Q7AQ71 | K07442 | No Hits | No Hits |
| 42 | Q7AQ59 | K06024 | No Hits | No Hits |
| 43 | Q7AQ55 | K07001 | No Hits | No Hits |
| 44 | Q9CC02 | K07006 | No Hits | No Hits |
| 45 | Q9CBW7 | K07005 | No Hits | No Hits |
| 46 | Q9CBW5 | K12574 | ko03018 RNA degradation | rnj; ribonuclease J [EC:3.1.-.-] |
| 47 | Q7AQ37 | K15634 | ko01100 Metabolic pathways<br>ko01110 Biosynthesis of secondary metabolites<br>ko01120 Microbial metabolism in diverse environments<br>ko01200 Carbon metabolism<br>ko01230 Biosynthesis of amino acids<br>ko00010 Glycolysis / Gluconeogenesis<br>ko00680 Methane metabolism<br>ko00260 Glycine, serine and threonine metabolism | gpmB; probable phosphoglyceratemutase [EC:5.4.2.12] |
| 48 | Q9CB84 | K07098 | No Hits | No Hits |
| 49 | Q7APW5 | K07009 | No Hits | No Hits |
| 50 | Q9CB74 | K00574 | No Hits | No Hits |

**Homology based metabolic pathway reconstruction:** Sequence information for metabolic pathway was retrieved from the KEGG database and MetaCyc [19]. Enzyme catalyzing each step in the reference metabolic pathway was used as query to search against UniProt-KB database for homologs in M. Leprae TN using NCBI protein blast (BLASTP) at an e value of $10^{-3}$. Hits

considered as true positive (homologs), when it had an identity of >30% and a coverage of >70%. Further, homologs founds within *M. leprae* TN were using COG modules of String database to understand the conservation of gene. Resultant, we found that inositol phosphate metabolism, fatty acid degradation, ethylbenzene degradation, sulfur relay system and limonene and pinene degradation were common metabolic pathways, which might be used as drug target in *M. leprae*. Here we reconstruct the Inositol phosphate metabolism because it is a common drug target in various Prokaryotes as well as in cancer cell.

**Case study: Inositol phosphate metabolism:** Inositol phosphate metabolism is common in eukaryotes, but it is also found in some prokaryotes. Inositol derivatives play an important role in *Mycobacteria*; they are glycosyl-phosphatidylinositol (GPI), phosphatidylinositol mannosides (PIM) and phosphatidylinositol (PI) [20]. Myo-inositol-1-phosphate (MIP) synthase is a good target for antipolar drugs [21]. *Mycobacterium tuberculosis, Trypanosomabrucei* and *Candida albicans* able to produce inositol in vitro in order to cause disease or even grow (*Trypanosomabrucei*) [22]. Hence, inositol phosphate metabolism is a possible drug target for *Mycobacteria*. We constructed the possible inositol phosphate synthetic pathway in *M. leprae*. Reference pathway for inositol phosphate synthesis is shown in supplementary **Fig. 1** and complete list of enzymes that are involved in inositol phosphate synthesis is shown in supplementary **Table 4.** Homology based possible inositol synthesis pathway in *M. leprae* was depicted in **Fig. 2**.

**Supplementary:**

**TABLE 4: LIST OF ENZYMES THAT ARE INVOLVED IN INOSITOL PHOSPHATE SYNTHESIS INOSITOL PHOSPHATE METABOLISM**

| Steps | EC No. of Enzyme | Homolog with mtb** | Enzyme (mle***) | COG (of Homolog) | COG (of mle) |
|---|---|---|---|---|---|
| Step1 | 5.5.1.4 | L0NNX2 | Q57240 | COG1260 | COG1260 |
| Step2 | 3.1.3.25 | L0NSZ7 | P46813 | COG0483 | COG0483 |

** mtb=*Mycobacterium* tuberculosis 1435

*** mle= *Mycobacterium* leprae TN

**Supplementary:**

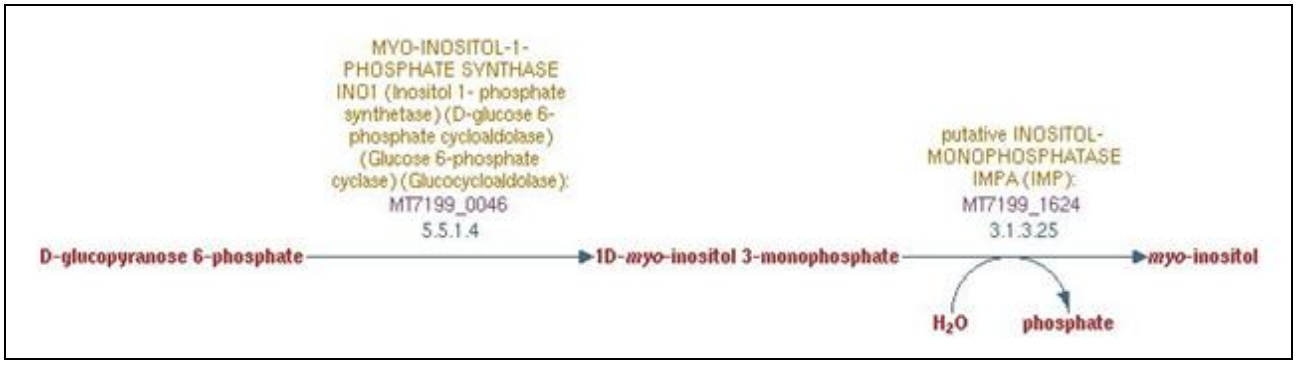


**FIG. 1: REFERENCE PATHWAY FOR INOSITOL PHOSPHATE SYNTHESIS**

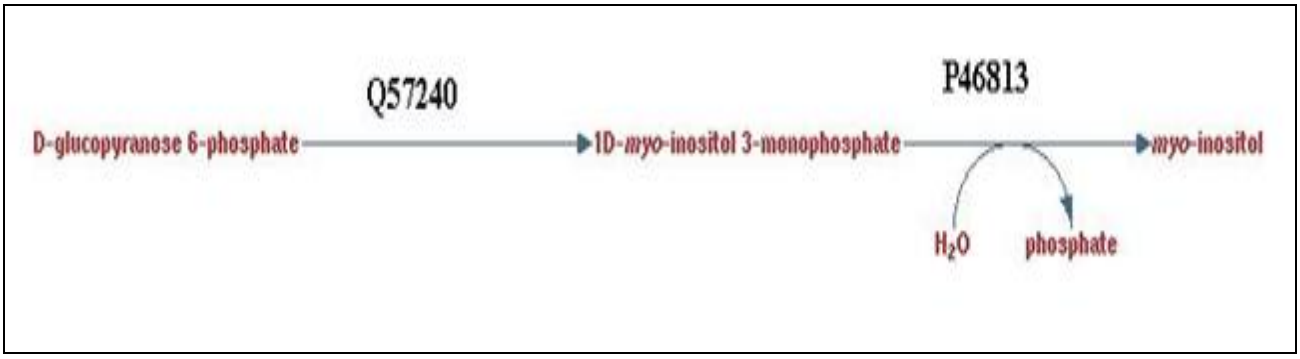


**FIG. 2: REPRESENTATION OF HOMOLOGY BASED INOSITOL SYNTHESIS PATHWAY IN *M. LEPRAE***

Interaction of query protein against COG was depicted in **Fig. 3A** and Phylogenetic analysis of query with other COG proteins were depicted in **Fig. 3-B**. There are two enzymes, Q57240 (COG1260) andP46813 (COG0483), which catalyzes the reactions in inositol phosphate synthesis and are conserved in *M. leprae*. Out of these two proteins, one protein (Q57240) is a hypothetical protein.

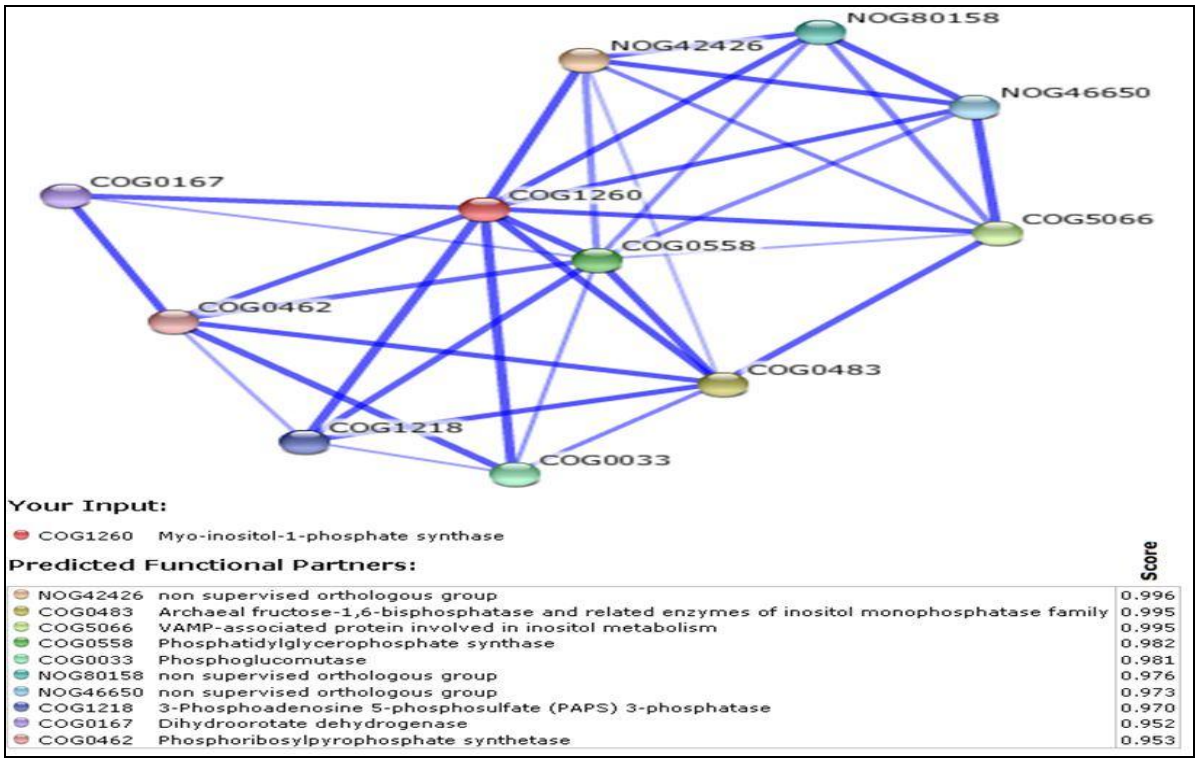


**FIG. 3A: NETWORK ANALYSIS OF QUERY PROTEIN SEARCHED AGAINST COG USING STRING**

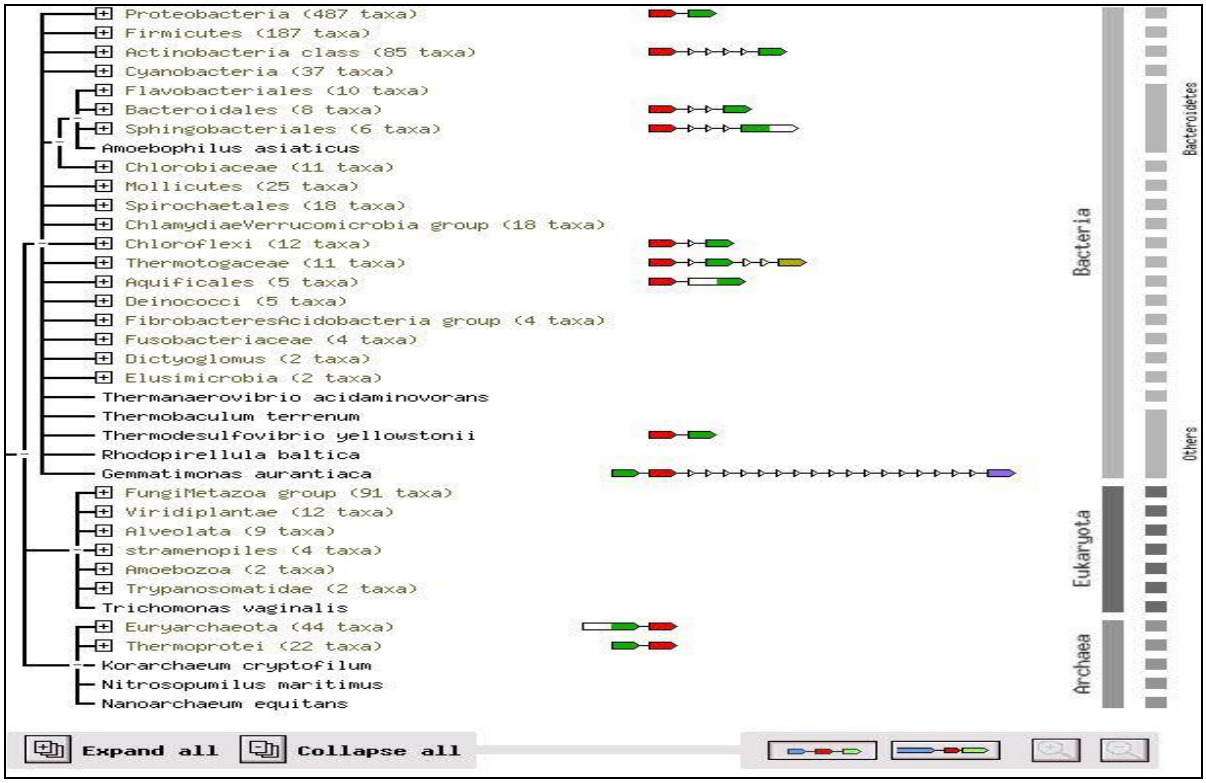


**FIG. 3B: PHYLOGENETIC ASSOCIATION OF QUERY PROTEIN AGAINST COG PROTEINS**

**CONCLUSION:** Sequence based possible drug target for *M. leprae* has been identified by computational approach [23, 24, 25]. 1603 protein sequences for *M. leprae* were present in UniProt-KB database, out of which, a staggering 27% and more remains classified as a hypothetical uncharacterized set of proteins. Out of these hypothetical uncharacterized set of proteins, 177 set of proteins had GO term. Out of these 177 protein sequences, 43 had DO term while 13 (out of these 43 sequences) were having homology with human proteome. Remaining 30 hypothetical uncharacterized protein sequences were observed which had DO term but were not homologous with human proteome [26, 27]. Thus, the 30 uncharacterized proteins may be used as putative drug target for *M. leprae*.

Out of 177 protein sequences which had GO term, 101 sequences displayed homology with Prokaryotes. These 101 sequences were found to be homologous with 494 DEG genes. KASS was used to predict Pathway associations for these 177 sequences and we found that 50 sequences had KEGG orthology hits. Out of 50, 15 sequences are found to be associated with 39 KEGG pathways [28, 29]. These protein sequences regulated the various metabolic pathways [30]. However, out of 39 pathways, inositol phosphate metabolism, fatty acid degradation, ethyl-benzene degradation, sulfur relay system and limonene & pinene degradation were common metabolic pathway, which might be used as putative drug target for *M. leprae*. Further, we reconstructed the homology based inositol metabolic pathway for *M. leprae*.

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