Research Article

Mycobacterium tuberculosis H37Rv: In Silico Drug Targets Identification by Metabolic Pathways Analysis

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Mycobacterium tuberculosis (Mtb) is a pathogenic bacteria species in the genus Mycobacteria and the causative agent of most cases of tuberculosis. Tuberculosis (TB) is the leading cause of death in the world from a bacterial infectious disease. This antibiotic resistance strain lead to development of the new antibiotics or drug molecules which can kill or suppress the growth of Mycobacterium tuberculosis. We have performed an in silico comparative analysis of metabolic pathways of the host Homo sapiens and the pathogen Mycobacterium tuberculosis (H37Rv). Novel efforts in developing drugs that target the intracellular metabolism of M. tuberculosis often focus on metabolic pathways that are specific to M. tuberculosis. We have identified five unique pathways for Mycobacterium tuberculosis having a number of 60 enzymes, which are nonhomologous to Homo sapiens protein sequences, and among them there were 55 enzymes, which are nonhomologous to Homo sapiens protein sequences. These enzymes were also found to be essential for survival of the Mycobacterium tuberculosis according to the DEG database. Further, the functional analysis using Uniprot showed involvement of all the unique enzymes in the different cellular components.

1. Introduction

Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB), remains a major health threat. Each year, 8 million new TB cases appear and 2 million individuals die of TB [1]. Further, about half a million new multidrug resistant TB cases are estimated to occur every year [2]. The existing drugs, although of immense value in controlling the disease to the extent that is being done today, have several shortcomings, the most important of them being the emergence of drug resistance rendering even the frontline drugs inactive. In addition, drugs such as rifampicin have high levels of adverse effects making them prone to patient incompliance. Another important problem with most of the existing antimycobacterials is their inability to act upon latent forms of the bacillus. In addition to these problems, the vicious interactions between the HIV (human immunodeficiency virus) and TB have led to further challenges for antitubercular drug discovery [3].

Recently, genome-scale metabolic network reconstructions for different organisms have enabled systematic analyses of metabolic functions and predictions of metabolism-related phenotypes. By collecting all possible biochemical reactions for specific organisms, different groups have reconstructed metabolic networks for bacteria, for example, Escherichia coli, Helicobacter pylori, and Chromohalobacter salexigens, eukaryotic microorganisms, mice, and even humans [4–6]. The website of the Systems Biology Research Group at the University of California, San Diego (http://gcrg.ucsd.edu/), provides a continuously updated list of genome-scale metabolic network reconstructions. Analysis of metabolic networks can provide insights into an organism’s ability to grow under specific conditions. For example, given a specific set of nutrient conditions, flux
Table 1: Unique pathways of *M. tuberculosis* when compared to *H. sapiens*.

| S. no. | Pathway name                                      | Human | *Mycobacterium tuberculosis H37Rv* |
|-------|--------------------------------------------------|-------|-----------------------------------|
| 1     | Carbohydrate Metabolism                          |       |                                   |
| 1.1   | C5-Branched dibasic acid metabolism              | Absent| Present                           |
| 2     | Energy Metabolism                                 |       |                                   |
| 2.1   | Photosynthesis                                    | Absent| Absent                            |
| 2.2   | Carbon fixation pathways in prokaryotes           | Absent| Present                           |
| 2.3   | Methane metabolism                               | Absent| Present                           |
| 3     | Lipid Metabolism                                  |       |                                   |
| 3.1   | Fatty acid elongation in mitochondria             | Present| Absent                           |
| 3.2   | Sphingolipid metabolism                          | Present| Absent                           |
| 3.3   | Arachidonic acid metabolism                       | Present| Absent                           |
| 4     | Nucleotide Metabolism                             |       |                                   |
| 4.1   | All Present                                      | All Present| All Present                   |
| 5     | Amino Acid Metabolism                             |       |                                   |
| 6     | Metabolism of Other Amino Acids                   |       |                                   |
| 6.1   | Phosphonate and phosphate metabolism              | Absent| Absent                            |
| 7     | Glycan Biosynthesis and Metabolism                |       |                                   |
| 7.1   | N-Glycan biosynthesis                            | Present| Absent                           |
| 7.2   | Various types of N-glycan biosynthesis            |       |                                   |
| 7.3   | Mucin type O-Glycan biosynthesis                 | Present| Absent                           |
| 7.4   | Other types of O-glycan biosynthesis             | Present| Absent                           |
| 7.5   | Glycosaminoglycan biosynthesis—chondroitin sulfate| Present| Absent                           |
| 7.6   | Glycosaminoglycan biosynthesis—heparan sulfate    | Present| Absent                           |
| 7.7   | Glycosaminoglycan biosynthesis—keratan sulfate    | Present| Absent                           |
| 7.8   | Glycosaminoglycan degradation                     | Present| Absent                           |
| 7.9   | Glycosylphosphatidylinositol (GPI)-anchor biosynthesis| Present| Absent                           |
| 7.10  | Glycosphingolipid biosynthesis—lacto and neolacto series | Present| Absent                           |
| 7.11  | Glycosphingolipid biosynthesis—globo series       | Present| Absent                           |
| 7.12  | Glycosphingolipid biosynthesis—ganglio series     | Present| Absent                           |
| 7.13  | Lipopolysaccharide biosynthesis                   | Absent| Present                           |
| 7.14  | Peptidoglycan biosynthesis                        | Absent| Present                           |
| 7.15  | Other Glycan degradation                          | Present| Absent                           |

balance analysis (FBA) of metabolic networks can accurately predict microbial cellular growth rates. In a recent work, a group of researchers used an approximate representation of in-host nutrient availability inferred from the literature to simulate the in-host metabolism of *Salmonella typhimurium* [7]. Moreover, metabolic network analyses can then be used to identify organism-specific essential genes by predicting the attenuation of microbial growth of specific deletion mutants [8–10].

The computational approach has been used to investigate novel drug targets in other pathogenic organisms such as *Pseudomonas aeruginosa* and in *Helicobacter pylori* [5, 11].

As most currently known, antibacterials are essentially inhibitors of certain bacterial enzymes; all enzymes specific to bacteria can be considered as potential drug targets [12]. In this study, we have adopted a strategy for comparative metabolic pathway analysis to find out some potential targets against *M. tuberculosis* (H37Rv). Only those enzymes which show unique properties than the host were selected as the target. Metabolic genes that are essential for pathogen growth but are not present in humans constitute actual and potential drug targets.

2. Materials and Methods

KEGG (Kyoto Encyclopedia of Gene and Genome) (http://www.genome.jp/pathways.html) [13] pathway database was used as a source of metabolic pathway information. Metabolic pathway identification numbers of the host *H. sapiens* and the pathogen *M. tuberculosis* (H37Rv) were extracted from the KEGG database. Pathways which do not appear in the host but are present in the pathogen according to KEGG database have been identified as pathways unique to *M. tuberculosis* as in comparison to the host *H. sapiens*. Enzymes in these unique pathways as well as enzymes involved in other metabolic pathways under carbohydrate metabolism, energy metabolism, lipid metabolism, nucleotide metabolism, amino acid metabolism, metabolism of other amino acids, and glycan biosynthesis were identified from the KEGG database. The corresponding protein sequences of enzymes involved in unique pathways were
Table 2: Essential enzymes using DEG.

| S. no. | Entry no. | Protein name                                                                 | Essential enzyme |
|-------|-----------|------------------------------------------------------------------------------|------------------|
| 1     | Rv1820    | Acetolactate synthase                                                        | Yes              |
| 2     | Rv0951    | Succinyl-CoA synthetase subunit beta                                         | Yes              |
| 3     | Rv2987c   | Isopropylmalate isomerase small subunit                                      | Yes              |
| 4     | Rv1475c   | Aconitate hydratase (EC: 4.2.1.3)                                            | Yes              |
| 5     | Rv0066c   | Isocitrate dehydrogenase (EC: 1.1.1.42)                                      | Yes              |
| 6     | Rv2454c   | 2-Oxoglutarate ferredoxin oxidoreductase subunit beta (EC: 1.2.7.3)          | Yes              |
| 7     | Rv1240    | Malate dehydrogenase (EC: 1.1.1.37)                                         | Yes              |
| 8     | Rv098c    | Fumarate hydratase (EC: 4.2.1.2)                                             | Yes              |
| 9     | Rv0247c   | Fumarate reductase iron-sulfur subunit (EC: 1.3.99.1)                        | Yes              |
| 10    | Rv3356c   | Bifunctional 5,10-methylene-tetrahydrofolate dehydrogenase/5,10-methylene-tetrahydrofolate Cyclohydrolase (EC: 1.5.1.5 3.5.4.9) | Yes              |
| 11    | Rv0951    | Succinyl-CoA synthetase subunit beta (EC: 6.2.1.5)                           | Yes              |
| 12    | Rv0904c   | Putative acetyl-coenzyme A carboxylase carboxyl transferase subunit beta (EC: 6.4.1.2) | Yes              |
| 13    | Rv0973c   | Acetyl-/propionyl-coenzyme A carboxylase subunit alpha (EC: 6.3.4.14)        | Yes              |
| 14    | Rv1492    | Methylmalonyl-CoA mutase small subunit (EC: 5.4.99.2)                        | Yes              |
| 15    | Rv3667    | Acetyl-CoA synthetase (EC: 6.2.1.1)                                          | Yes              |
| 16    | Rv0409    | Acetate kinase (EC: 2.7.2.1)                                                 | Yes              |
| 17    | Rv0408    | Phosphate acetyltransferase (EC: 2.3.1.8)                                    | Yes              |
| 18    | Rv0243    | Acetyl-CoA acetyltransferase (EC: 2.3.1.9)                                   | Yes              |
| 19    | Rv0860    | Fatty oxidation protein FadB                                                  | Yes              |
| 20    | Rv3667    | Acetyl-CoA synthetase (EC: 6.2.1.1)                                          | Yes              |
| 21    | Rv0373c   | Carbon monoxide dehydrogenase large subunit (EC: 1.2.99.2)                  | No               |
| 22    | Rv2900c   | Formate dehydrogenase H (EC: 1.2.1.2)                                        | No               |
| 23    | Rv1023    | Phosphopyruvate hydratase (EC: 4.2.1.11)                                     | Yes              |
| 24    | Rv1240    | Malate dehydrogenase (EC: 1.1.1.37)                                         | Yes              |
| 25    | Rv0070c   | Serine hydroxymethyltransferase (EC: 2.1.2.1)                                | Yes              |
| 26    | Rv2205c   | Hypothetical protein                                                          | Yes              |
| 27    | Rv0761c   | Zinc-containing alcohol dehydrogenase NAD dependent AdhB (EC: 1.1.1.1)       | Yes              |
| 28    | Rv0489    | Phosphoglyceromutase (EC: 5.4.2.1)                                           | Yes              |
| 29    | Rv0363c   | Fructose-bisphosphate aldolase (EC: 4.1.2.13)                                | Yes              |
| 30    | Rv0292c   | Phosphofructokinase Pi&K (phosphohexokinase) (EC: 2.7.1.—)                  | Yes              |
| 31    | Rv1908c   | Catalase-peroxidase-peroxynitritase T KatG (EC: 1.1.1.6)                      | Yes              |
| 32    | Rv0070c   | Serine hydroxymethyltransferase (EC: 2.1.2.1)                                | Yes              |
| 33    | Rv0728c   | D-3-phosphoglycerate dehydrogenase (EC: 1.1.1.95)                            | Yes              |
| 34    | Rv0505c   | Phosphoserine phosphatase (EC: 3.1.3.3)                                      | Yes              |
| 35    | Rv0884c   | Phosphoserine aminotransferase (EC: 2.6.1.52)                                | Yes              |
| 36    | Rv0409    | Acetate kinase (EC: 2.7.2.1)                                                 | Yes              |
| 37    | Rv0408    | Phosphate acetyltransferase (EC: 2.3.1.8)                                    | Yes              |
| 38    | Rv3667    | Acetyl-CoA synthetase (EC: 6.2.1.1)                                          | Yes              |
| 39    | Rv2611c   | Lipid A biosynthesis lauroyl acyltransferase (EC: 2.3.1. —)                  | Yes              |
| 40    | Rv0114    | D-alpha,beta-D-heptose-1,7-biphosphate phosphatase (EC: 2. —,—,—,—)         | Yes              |
| 41    | Rv0113    | Phosphoheptose isomerase (EC: 5. —,—,—,—)                                   | Yes              |
| 42    | Rv1315    | UDP-N-acetylglucosamine 1-carboxyvinyltransferase (EC: 2.5.1.7)              | Yes              |
| 43    | Rv0482    | UDP-N-acetylglucosaminylpyruvylglucosamine reductase (EC: 1.1.1.158)         | Yes              |
| 44    | Rv2152c   | UDP-N-acetylmuramate-L-alanine ligase (EC: 6.3.2.8)                           | Yes              |
| 45    | Rv2155c   | UDP-N-acetylmuramoyl-L-alanyl-L-glutamate synthetase (EC: 6.3.2.9)            | Yes              |
| 46    | Rv2157c   | UDP-N-acetylmuramoylalanyl-L-glutamy-2,6-diaminopimelate-D-alanyl-D-alanyl ligase MurF | Yes              |
Table 2: Continued.

| S. no. | Entry no. | Protein name | Essential enzyme |
|--------|------------|--------------|------------------|
| 47.    | Rv2156c    | Phospho-N-acetylmuramoyl-pentapeptide-transferase (EC: 2.7.8.13) | Yes |
| 48.    | Rv2153c    | Undecaprenyldiphospho-muramoylpentapeptide beta-N-acetylglucosaminyltransferase (EC: 2.4.1.227) | Yes |
| 49.    | Rv2911     | D-alanyl-D-alanine carboxypeptidase (EC: 3.4.16.4) | No |
| 50.    | Rv2981c    | D-alanyl-alanine synthetase A (EC: 6.3.2.4) | Yes |
| 51.    | Rv2136c    | Undecaprenylpyrophosphate phosphatase (EC: 3.1.3.1) | Yes |
| 52.    | Rv2911     | D-alanyl-D-alanine carboxypeptidase (EC: 3.4.16.4) | No |
| 53.    | Rv2158c    | UDP-N-acetylmuramoylalanine-D-glutamate-2,6-diaminopimelate ligase (EC: 6.3.2.13) | Yes |
| 54.    | Rv2157c    | UDP-N-acetylmuramoylalanine-D-glutamyl-2,6-diaminopimelate-D-alanyl-D-alanyl ligase MurF | Yes |
| 55.    | Rv2156c    | Phospho-N-acetylmuramoyl-pentapeptide-transferase (EC: 2.7.8.13) | Yes |
| 56.    | Rv2153c    | Undecaprenyldiphospho-muramoylpentapeptide beta-N-acetylglucosaminyltransferase (EC: 2.4.1.227) | Yes |
| 57.    | Rv3910     | Transmembrane protein | Yes |
| 58.    | Rv0016c    | Penicillin-binding protein PbpA | Yes |
| 59.    | Rv2163c    | Penicillin-binding membrane protein PbpB | Yes |
| 60.    | Rv2911     | D-alanyl-D-alanine carboxypeptidase (EC: 3.4.16.4) | No |

identified and their protein sequences were retrieved in FASTA format from KEGG database.

The unique enzymes were further analyzed for essentiality to pathogen by DEG (Database of Essential Genes) database (http://tubic.tju.edu.cn/deg/) [14], and considered cutoff score was >100 to enhance the specificity of enzyme in *M. tuberculosis*.

The obtained targets genes were further analyzed by UniProt (Universal Protein Resource) (http://www.uniprot.org/) database to find out their functions. This is required to find out the surface membrane proteins which could be probable vaccine targets.

### 3. Results and Discussion

**3.1. Identification of Unique Pathways and Potential Drug Targets.** Tuberculosis (TB) is a major cause of illness and death worldwide, especially in Asia and Africa. Globally, 9.2 million new cases and 1.7 million deaths from TB occurred in 2006, of which 0.7 million cases and 0.2 million deaths were in HIV-positive people [2]. The existing drugs have several shortcomings, the most important of them being the emergence of drug resistance.

No new anti-Mtb drugs have been developed for well over 20 years. In view of the increasing development of resistance to the current leading anti-Mtb drugs, novel strategies are desperately needed to avert the “global catastrophe” forecast by the WHO (World Health Organization). Therefore, computational approach for drug targets identification, specifically for *Mtb*, can produce a list of reliable targets very rapidly. These methods have the advantage of speed and low cost and, even more importantly, provide a systems view of the whole microbe at a time. Since it is generally believed that the genomes of bacteria contain genes both with and without homologues to the human host. Using computational approach for target identification it is very quick to produce a desirable list.

In the present study, 5 unique pathways, C5-branched dibasic acid metabolism, carbon fixation pathways in prokaryotes, methane metabolism, lipopolysaccharide biosynthesis, and peptidoglycan biosynthesis with 60 new nonhomologous targets were identified through *in silico* comparative metabolic pathway analysis of *Homo sapiens* and *M. tuberculosis* H37Rv using KEGG database. Pathways which are not present in the *Homo sapiens* but present in the Mycobacterium are designated as unique pathways. Design and targeting inhibitors against these nonhomologous sequences could be the better approach for generation of new drugs. Thus total 5 unique metabolic pathways have been taken in *M. tuberculosis* (Table 1).

**3.2. Identification of Essential Genes.** Essential genes are those indispensable for the survival of an organism, and their functions are, therefore, considered a foundation of life. Total 55 enzymes out of all were found to be essential for *M. tuberculosis* life cycle (Table 2). These targets were found to be potential targets and could be considered for rational drug design. Using metabolic pathway information as the starting point for the identification of potential targets has its advantages as each step in the pathway is validated as the essential function for the survival of the bacterium.

**3.3. Identification of Drug Target's Functions Using UniProt.** The subcellular localization analysis of all supposed essential and unique enzymes of *M. tuberculosis* were evaluated by UniProt server. As it was suggested that, membrane associated protein could be the better target for developing vaccines. After functional analysis unique enzymes involved in cellular components like cell wall, cytoplasm, extracellular region, plasma membrane, and so forth, their biological processes and their functions have been retrieved (Table 3).
### Table 3: Shows function of all Essential proteins.

| S. no. | Accession no. | Cellular component | Molecular function | Biological process |
|--------|---------------|--------------------|--------------------|--------------------|
| 1      | Rv1820        | Not known          | Acetolactate synthase activity, magnesium ion binding, thiamine pyrophosphate binding | Branched chain family amino acid biosynthetic process |
| 2      | Rv0951        | Cell wall, cytosol | ATP binding, metal ion binding, succinate-CoA ligase (ADP-forming) activity | Growth, tricarboxylic acid cycle |
| 3      | Rv2987c       | Plasma membrane, 3-isopropylmalate dehydratase complex | 3-Isopropylmalate dehydratase activity | Growth, leucine biosynthetic process |
| 4      | Rv1475c       | Cell wall, cytosol, extracellular region, plasma membrane | 4 iron, 4 sulfur cluster binding, aconitate hydratase activity, iron-responsive element binding | Growth, response to iron ion |
| 5      | Rv0066c       | Cytosol, extracellular region, plasma membrane | NAD binding, isocitrate dehydrogenase (NADP+) activity, magnesium ion binding, protein homodimerization activity | Tricarboxylic acid cycle |
| 6      | Rv2454c       | Cell wall, cytosol | 2-Oxoglutarate synthase activity, magnesium ion binding, thiamine pyrophosphate binding | Oxidation-reduction process |
| 7      | Rv1240        | Cytosol, plasma membrane | L-malate dehydrogenase activity, binding | Glycolysis, malate metabolic process, tricarboxylic acid cycle |
| 8      | Rv1098c       | Cytosol, extracellular region, plasma membrane | Electron carrier activity, iron-sulfur cluster binding, succinate dehydrogenase activity | Growth, tricarboxylic acid cycle |
| 9      | Rv0247c       | Plasma membrane | Electron carrier activity, iron-sulfur cluster binding, succinate dehydrogenase activity | Tricarboxylic acid cycle |
| 10     | Rv3356c       | Extracellular region, plasma membrane | Binding, methenyltetrahydrofolate cyclohydrolase activity, methenyltetrahydrofolate dehydrogenase (NADP+) activity | Folic acid-containing compound biosynthetic process, growth, histidine biosynthetic process |
| 11     | Rv0951        | Cell wall, cytosol | ATP binding, metal ion binding, succinate-CoA ligase (ADP-forming) activity | Growth, tricarboxylic acid cycle |
| 12     | Rv0904c       | Acetyl-CoA carboxylase complex, plasma membrane | ATP binding, acetyl-CoA carboxylase activity, protein binding | Mycolic acid biosynthetic process |
| 13     | Rv0973c       | Plasma membrane | ATP binding, biotin binding, biotin carboxylase activity | Growth |
| 14     | Rv1492        | Cell wall, cytosol, plasma membrane | Cobalamin binding, metal ion binding, methylmalonyl-CoA mutase activity | Lactate fermentation to propionate and acetate, propionate metabolic process, methylmalonyl pathway |
| 15     | Rv3667        | Cell wall, plasma membrane | AMP binding, ATP binding, acetate-CoA ligase activity | Not known |
| 16     | Rv0409        | Cytoplasm | ATP binding, acetate kinase activity | Organic acid metabolic process |
| 17     | Rv0408        | Cytoplasm, extracellular region | Phosphate acetyltransferase activity | Not known |
| 18     | Rv0243        | Cytosol, plasma membrane | Acetyl-CoA C-acyltransferase activity | Growth of symbiont in host cell |
| 19     | Rv0860        | Cytosol, plasma membrane | Coenzyme binding, oxidoreductase activity | Fatty acid metabolic process, oxidation-reduction process |
| 20     | Rv3667        | Cell wall, plasma membrane | AMP binding, ATP binding, acetate-CoA ligase activity | Not known |
| 21     | Rv1023        | Cell surface, extracellular region, phosphoprotocatehydratase complex, plasma membrane | Magnesium ion binding, phosphopyruvate hydratase activity | Glycolysis, growth |
| S. no. | Accession. no. | Cellular component | Biological process | Molecular function |
|-------|----------------|--------------------|--------------------|--------------------|
| 22.   | Rv1240         | Cytosol, plasma membrane | Glycolysis, malate metabolic process, tricarboxylic acid cycle | L-malate dehydrogenase activity, binding |
| 23.   | Rv0070c        | Not known          | Not known          | Not known          |
| 24.   | Rv2205c        | Not known          | Organic acid phosphorylation | Glycerate kinase activity |
| 25.   | Rv0761c        | Oxidation-reduction process | Cytoplasm, plasma membrane | Alcohol dehydrogenase (NAD) activity, zinc ion binding |
| 26.   | Rv0489         | Plasma membrane    | Glycolysis         | Phosphoglycerate mutase activity |
| 27.   | Rv0363c        | Extracellular region, plasma membrane | Glycolysis, protein homotetramerization | Fructose-bisphosphate aldolase activity, zinc ion binding |
| 28.   | Rv2029c        | Not known          | Carbohydrate metabolic process | Kinase activity, phosphotransferase activity, alcohol group as acceptor |
| 29.   | Rv1908c        | Not known          | Hydrogen peroxide catabolic process, oxidation-reduction process, response to antibiotic | Catalase activity, heme binding |
| 30.   | Rv0070c        | Not Known          | Not Known          | Not known          |
| 31.   | Rv0728c        | Not Known          | Oxidation-reduction process | NAD binding, phosphoglycerate dehydrogenase activity |
| 32.   | Rv0505c        | Integral to plasma membrane | Not Known          | Metal ion binding, phosphatase activity |
| 33.   | Rv0884c        | Cytoplasm, extracellular region, plasma membrane | L-serine biosynthetic process, growth, pyridoxine biosynthetic process | O-phospho-L-serine: 2-oxoglutarate aminotransferase activity, pyridoxal phosphate binding |
| 34.   | Rv0409         | Cytoplasm          | Organic acid metabolic process | ATP binding, acetate kinase activity |
| 35.   | Rv0408         | Cytoplasm, extracellular region | Not known          | Phosphate acetyltransferase activity |
| 36.   | Rv3667         | Cell wall, plasma membrane | Not known          | AMP binding, ATP binding, acetate-CoA ligase activity |
| 37.   | Rv2611c        | Integral to membrane, plasma membrane | Glycolipid biosynthetic process, growth, lipopolysaccharide core region biosynthetic process | Acyltransferase activity |
| 38.   | Rv0114         | Cytoplasm          | Carbohydrate metabolic process, histidine biosynthetic process | Histidinol-phosphatase activity |
| 39.   | Rv0113         | Cytoplasm          | Carbohydrate metabolic process | D-sedoheptulose 7-phosphate isomerase activity, metal ion binding, sugar binding |
| 40.   | Rv1315         | Cytoplasm          | UDP-N-acetylgalactosamine biosynthetic process, cell cycle, cell division, cellular cell wall organization, growth, peptidoglycan biosynthetic process, regulation of cell shape | UDP-N-acetylgalactosamine l-carboxyvinyltransferase activity |
| 41.   | Rv0482         | Cytoplasm          | UDP-N-acetylgalactosamine biosynthetic process, cell cycle, cell division, cellular cell wall organization, growth, peptidoglycan biosynthetic process, regulation of cell shape | UDP-N-acetylmuramylMuramylpeptidoglycan biosynthetic process, regulation of cell shape |
| 42.   | Rv2152c        | Cytoplasm          | UDP-N-acetylmuramylMuramylpeptidoglycan biosynthetic process, regulation of cell shape | UDP-N-acetylmuramylMuramylpeptidoglycan biosynthetic process, regulation of cell shape |
| 43.   | Rv2155c        | Cytosol            | ATP binding, UDP-N-acetylmuramylpeptidoglycan biosynthetic process, regulation of cell shape | ATP binding, UDP-N-acetylmuramylpeptidoglycan biosynthetic process, regulation of cell shape |
| S. no. | Accession no. | Cellular component | Biological process | Molecular function |
|--------|---------------|-------------------|--------------------|--------------------|
| 44.    | Rv2157c       | Cytoplasm         | Cell cycle, cell division, cellular cell wall organization, growth, peptidoglycan biosynthetic process, regulation of cell shape | ATP binding, UDP-N-acetylmuramoyl-tripeptide-D-alanyl-D-alanine ligase activity, UDP-N-acetylmuramoylalanyl-D-glutamyl-2,6-diaminopimelate-D-alanyl-D-alanine ligase activity |
| 45.    | Rv2156c       | Integral to membrane, plasma membrane | Cell cycle, cell division, cellular cell wall organization, growth, peptidoglycan biosynthetic process, regulation of cell shape | Phospho-N-acetylmuramoyl-pentapeptide-transferase activity |
| 46.    | Rv2153c       | Plasma membrane   | Cell cycle, cell division, cellular cell wall organization, growth, regulation of cell shape, UDP-N-acetylgalactosamine biosynthetic process, lipid glycosylation, peptidoglycan biosynthetic process | Carbohydrate binding, undecaprenyldiphospho-muramoylpentapeptide beta-N-acetylglicosaminyltransferase activity |
| 47.    | Rv2981c       | Cell wall, cytoplasm, plasma membrane | Cellular cell wall organization, growth, peptidoglycan biosynthetic process, regulation of cell shape | ATP binding, D-alanine-D-alanine ligase activity, metal ion binding |
| 48.    | Rv2136c       | Integral to membrane, plasma membrane | Cellular cell wall organization, peptidoglycan biosynthetic process, regulation of cell shape, dephosphorylation, response to antibiotic, response to nitrosative stress | Undecaprenyl-diphosphatase activity |
| 49.    | Rv2158c       | Cytosol, plasma membrane | Cell cycle, cell division, cellular cell wall organization, peptidoglycan biosynthetic process, regulation of cell shape | ATP binding, UDP-N-acetylmuramoylalanyl-D-glutamate-2,6-diaminopimelate ligase activity, ATP binding, UDP-N-acetylmuramoyl-alanyl-D-alanine ligase activity |
| 50.    | Rv2157c       | Cytoplasm         | Cell cycle, cell division, cellular cell wall organization, growth, peptidoglycan biosynthetic process, regulation of cell shape | ATP binding, UDP-N-acetylmuramoyl-tripeptide-D-alanyl-D-alanine ligase activity |
| 51.    | Rv2156c       | Integral to membrane, plasma membrane | Cell cycle, cell division, cellular cell wall organization, growth, peptidoglycan biosynthetic process, regulation of cell shape | Phospho-N-acetylmuramoyl-pentapeptide-transferase activity |
| 52.    | Rv2153c       | Plasma membrane   | Cell cycle, cell division, cellular cell wall organization, growth, peptidoglycan biosynthetic process, regulation of cell shape, UDP-N-acetylgalactosamine biosynthetic process | Carbohydrate binding, undecaprenyldiphospho-muramoylpentapeptide beta-N-acetylglicosaminyltransferase activity |
| 53.    | Rv3910        | Integral to plasma membrane | Not known | Not known |
| 54.    | Rv0016c       | Cell septum, cytosol, integral to membrane, plasma membrane | Cellular cell wall organization, peptidoglycan biosynthetic process, regulation of cell shape | Penicillin binding, transferase activity |
| 55.    | Rv2163c       | Extracellular region | Growth, peptidoglycan-based cell wall biogenesis | Penicillin binding, protein binding |
In conclusion, the computational genomic approach has facilitated the search for potential drug targets against *M. tuberculosis*. Use of the DEG database is more efficient than conventional methods for identification of essential genes and it facilitates the exploratory identification of the most relevant drug targets in the pathogen. The current study can be carried forward to design a drug that can block these drug targets. The microorganisms are fast in gaining resistance to the existing drugs, so designing better and effective drugs needs a faster method.

**Appendix**

See Tables 1, 2, and 3.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

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