Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence

S. T. Cole*, R. Brosch*, J. Parkhill, T. Garnier*, C. Churcher, D. Harris, S. V. Gordon*, K. Eiglmeier*, S. Gas*, C. E. Barry III†, F. Tekaia‡, K. Badcock, D. Basham, D. Brown, T. Chillingworth, R. Connor, R. Davies, K. Devlin, T. Feltwell, S. Gentles, N. Hamlin, S. Holroyd, T. Hornsby, K. Jagels, A. Krogh§, J. McLean, S. Moule, L. Murphy, K. Oliver, J. Osborne, M. A. Quail, M.-A. Rajandream, J. Rogers, S. Rutter, K. Seeger, J. Skelton, R. Squares, S. Squares, J. E. Sulston, K. Taylor, S. Whitehead & B. G. Barrell

Sanger Centre, Wellcome Trust Genome Campus, Hinxton CB10 1SA, UK
** Unité de Génétique Moléculaire Bactérienne, and ‡ Unité de Génétique Moléculaire des Levures, Institut Pasteur, 28 rue du Docteur Roux, 75724 Paris Cedex 15, France*
† Tuberculosis Research Unit, Laboratory of Intracellular Parasites, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, Montana 59840, USA
§ Center for Biological Sequence Analysis, Technical University of Denmark, Lyngby, Denmark

Countless millions of people have died from tuberculosis, a chronic infectious disease caused by the tubercle bacillus. The complete genome sequence of the best-characterized strain of *Mycobacterium tuberculosis*, H37Rv, has been determined and analysed in order to improve our understanding of the biology of this slow-growing pathogen and to help the conception of new prophylactic and therapeutic interventions. The genome comprises 4,411,529 base pairs, contains around 4,000 genes, and has a very high guanine + cytosine content that is reflected in the biased amino-acid content of the proteins. *M. tuberculosis* differs radically from other bacteria in that a very large portion of its coding capacity is devoted to the production of enzymes involved in lipogenesis and lipolysis, and to two new families of glycine-rich proteins with a repetitive structure that may represent a source of antigenic variation.

Despite the availability of effective short-course chemotherapy (DOTS) and the Bacille Calmette-Guérin (BCG) vaccine, the tubercle bacillus continues to claim more lives than any other single infectious agent[1]. Recent years have seen increased incidence of tuberculosis in both developing and industrialized countries, the widespread emergence of drug-resistant strains and a deadly synergy with the human immunodeficiency virus (HIV). In 1993, the gravity of the situation led the World Health Organisation (WHO) to declare tuberculosis a global emergency in an attempt to heighten public and political awareness. Radical measures are needed now to prevent the grim predictions of the WHO becoming reality. The combination of genomics and bioinformatics has the potential to generate the information and knowledge that will enable the conception and development of new therapies and interventions needed to treat this airborne disease and to elucidate the unusual biology of its aetiological agent, *Mycobacterium tuberculosis*.

The characteristic features of the tubercle bacillus include its slow growth, dormancy, complex cell envelope, intracellular pathogenesis and genetic homogeneity[2]. The generation time of *M. tuberculosis*, in synthetic medium or infected animals, is typically ~24 hours. This contributes to the chronic nature of the disease, imposes lengthy treatment regimens and represents a formidable obstacle for researchers. The state of dormancy in which the bacillus remains quiescent within infected tissue may reflect metabolic shutdown resulting from the action of a cell-mediated immune response that can contain but not eradicate the infection. As immunity wanes, through ageing or immune suppression, the dormant bacteria reactivate, causing an outbreak of disease often many decades after the initial infection[3]. The molecular basis of dormancy and reactivation remains obscure but is expected to be genetically programmed and to involve intracellular signalling pathways.

The cell envelope of *M. tuberculosis*, a Gram-positive bacterium with a G + C-rich genome, contains an additional layer beyond the peptidoglycan that is exceptionally rich in unusual lipids, glycolipids and polysaccharides[4,5]. Novel biosynthetic pathways generate cell-wall components such as mycolic acids, mycocerosic acid, phenolthiocerol, lipoarabinomannan and arabinogalactan, and several of these may contribute to mycobacterial longevity, trigger inflammatory host reactions and act in pathogenesis. Little is known about the mechanisms involved in life within the macrophage, or the extent and nature of the virulence factors produced by the bacillus and their contribution to disease.

It is thought that the progenitor of the *M. tuberculosis* complex, comprising *M. tuberculosis*, *M. bovis*, *M. bovis* BCG, *M. africanum* and *M. microti*, arose from a soil bacterium and that the human bacillus may have been derived from the bovine form following the domestication of cattle. The complex lacks interstrain genetic diversity, and nucleotide changes are very rare[6]. This is important in terms of immunity and vaccine development as most of the proteins will be identical in all strains and therefore antigenic drift will be restricted. On the basis of the systematic sequence analysis of 26 loci in a large number of independent isolates[6], it was concluded that the genome of *M. tuberculosis* is either unusually inert or that the organism is relatively young in evolutionary terms.

Since its isolation in 1905, the H37Rv strain of *M. tuberculosis* has found extensive, worldwide application in biomedical research because it has retained full virulence in animal models of tuberculosis, unlike some clinical isolates; it is also susceptible to drugs and amenable to genetic manipulation. An integrated map of the 4.4 megabase (Mb) circular chromosome of this slow-growing pathogen had been established previously and ordered libraries of cosmids and bacterial artificial chromosomes (BACs) were available[7,8].

Organization and sequence of the genome

Sequence analysis. To obtain the contiguous genome sequence, a combined approach was used that involved the systematic sequence analysis of selected large-insert clones (cosmids and BACs) as well as

Nature © Macmillan Publishers Ltd 1998

random small-insert clones from a whole-genome shotgun library. This culminated in a composite sequence of 4,411,529 base pairs (bp) (Figs 1, 2), with a G + C content of 65.6%. This represents the second-largest bacterial genome sequence currently available (after that of *Escherichia coli*)[9]. The initiation codon for the *dnaA* gene, a hallmark for the origin of replication, *oriC*, was chosen as the start point for numbering. The genome is rich in repetitive DNA, particularly insertion sequences, and in new multigene families and duplicated housekeeping genes. The G + C content is relatively constant throughout the genome (Fig. 1) indicating that horizontally transferred pathogenicity islands of atypical base composition are probably absent. Several regions showing higher than average G + C content (Fig. 1) were detected; these correspond to sequences belonging to a large gene family that includes the polymorphic G + C-rich sequences (PGRSs).

Genes for stable RNA. Fifty genes coding for functional RNA molecules were found. These molecules were the three species produced by the unique ribosomal RNA operon, the 10Sa RNA involved in degradation of proteins encoded by abnormal messenger RNA, the RNA component of RNase P, and 45 transfer RNAs. No 4.5S RNA could be detected. The *rrn* operon is situated unusually as it occurs about 1,500 kilobases (kb) from the putative *oriC*; most eubacteria have one or more *rrn* operons near to *oriC* to exploit the gene-dosage effect obtained during replication[10]. This arrangement may be related to the slow growth of *M. tuberculosis*. The genes encoding tRNAs that recognize 43 of the 61 possible sense codons were distributed throughout the genome and, with one exception, none of these uses A in the first position of the anticodon, indicating that extensive wobble occurs during translation. This is consistent with the high G + C content of the genome and the consequent bias in codon usage. Three genes encoding tRNAs for methionine were found; one of these genes (*metV*) is situated in a region that may correspond to the terminus of replication (Figs 1, 2). As *metV* is linked to defective genes for integrase and excisionase, perhaps it was once part of a phage or similar mobile genetic element.

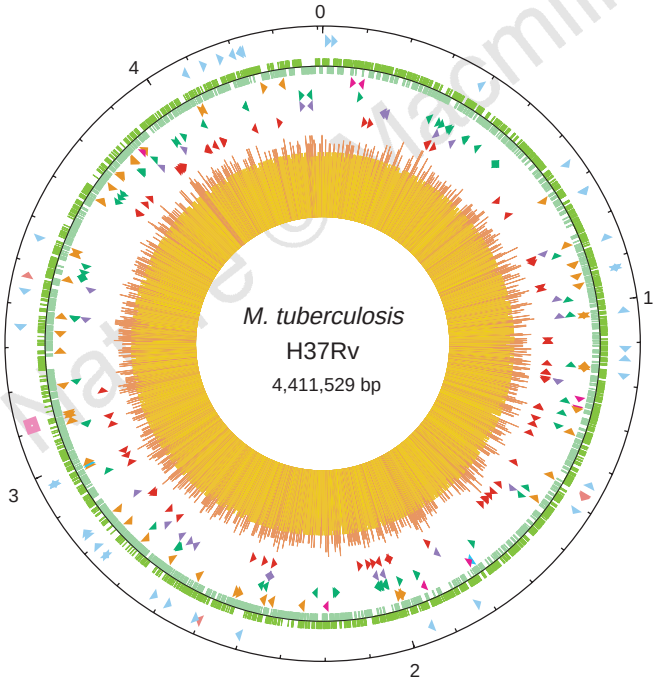


Figure 1 Circular map of the chromosome of *M. tuberculosis* H37Rv. The outer circle shows the scale in Mb, with 0 representing the origin of replication. The first ring from the exterior denotes the positions of stable RNA genes (tRNAs are blue, others are pink) and the direct repeat region (pink cube); the second ring inwards shows the coding sequence by strand (clockwise, dark green; anticlockwise, light green); the third ring depicts repetitive DNA (insertion sequences, orange; 13E12 REP family, dark pink; prophage, blue); the fourth ring shows the positions of the PPE family members (green); the fifth ring shows the PE family members (purple, excluding PGRS); and the sixth ring shows the positions of the PGRS sequences (dark red). The histogram (centre) represents G + C content, with <65% G + C in yellow, and >65% G + C in red. The figure was generated with software from DNASTAR.

Insertion sequences and prophages. Sixteen copies of the promiscuous insertion sequence IS*6110* and six copies of the more stable element IS*1081* reside within the genome of H37Rv[8]. One copy of IS*1081* is truncated. Scrutiny of the genomic sequence led to the identification of a further 32 different insertion sequence elements, most of which have not been described previously, and of the 13E12 family of repetitive sequences which exhibit some of the characteristics of mobile genetic elements (Fig. 1). The newly discovered insertion sequences belong mainly to the IS*3* and IS*256* families, although six of them define a new group. There is extensive similarity between IS*1561* and IS*1552* with insertion sequence elements found in *Nocardia* and *Rhodococcus* spp., suggesting that they may be widely disseminated among the actinomycetes.

Most of the insertion sequences in *M. tuberculosis* H37Rv appear to have inserted in intergenic or non-coding regions, often near tRNA genes (Fig. 1). Many are clustered, suggesting the existence of insertional hot-spots that prevent genes from being inactivated, as has been described for *Rhizobium*[11]. The chromosomal distribution of the insertion sequences is informative as there appears to have been a selection against insertions in the quadrant encompassing *oriC* and an overrepresentation in the direct repeat region that contains the prototype IS*6110*. This bias was also observed experimentally in a transposon mutagenesis study[12].

At least two prophages have been detected in the genome sequence and their presence may explain why *M. tuberculosis* shows persistent low-level lysis in culture. Prophages phiRv1 and phiRv2 are both ~10 kb in length and are similarly organized, and some of their gene products show marked similarity to those encoded by certain bacteriophages from *Streptomyces* and saprophytic mycobacteria. The site of insertion of phiRv1 is intriguing as it corresponds to part of a repetitive sequence of the 13E12 family that itself appears to have integrated into the biotin operon. Some strains of *M. tuberculosis* have been described as requiring biotin as a growth supplement, indicating either that phiRv1 has a polar effect on expression of the distal *bio* genes or that aberrant excision, leading to mutation, may occur. During the serial attenuation of *M. bovis* that led to the vaccine strain *M. bovis* BCG, the phiRv1 prophage was lost[13]. In a systematic study of the genomic diversity of prophages and insertion sequences (S.V.G. *et al.*, manuscript in preparation), only IS*1532* exhibited significant variability, indicating that most of the prophages and insertion sequences are currently stable. However, from these combined observations, one can conclude that horizontal transfer of genetic material into the free-living ancestor of the *M. tuberculosis* complex probably occurred in nature before the tubercle bacillus adopted its specialized intracellular niche.

Figure 2 Linear map of the chromosome of *M. tuberculosis* H37Rv showing the position and orientation of known genes and coding sequences (CDS). We used the following functional categories (adapted from ref. 20): lipid metabolism (black); intermediary metabolism and respiration (yellow); information pathways (pink); regulatory proteins (sky blue); conserved hypothetical proteins (orange); proteins of unknown function (light green); insertion sequences and phage-related functions (blue); stable RNAs (purple); cell wall and cell processes (dark green); PE and PPE protein families (magenta); virulence, detoxification and adaptation (white). For additional information about gene functions, refer to http://www.sanger.ac.uk. ▶

Nature © Macmillan Publishers Ltd 1998

Genes encoding proteins. 3,924 open reading frames were identified in the genome (see Methods), accounting for ~91% of the potential coding capacity (Figs 1, 2). A few of these genes appear to have in-frame stop codons or frameshift mutations (irrespective of the source of the DNA sequenced) and may either use frameshifting during translation or correspond to pseudogenes. Consistent with the high G + C content of the genome, GTG initiation codons (35%) are used more frequently than in *Bacillus subtilis* (9%) and *E. coli* (14%), although ATG (61%) is the most common translational start. There are a few examples of atypical initiation codons, the most notable being the ATC used by *infC*, which begins with ATT in both *B. subtilis* and *E. coli*[9,14]. There is a slight bias in the orientation of the genes (Fig. 1) with respect to the direction of replication as ~59% are transcribed with the same polarity as replication, compared with 75% in *B. subtilis*. In other bacteria, genes transcribed in the same direction as the replication forks are believed to be expressed more efficiently[9,14]. Again, the more even distribution in gene polarity seen in *M. tuberculosis* may reflect the slow growth and infrequent replication cycles. Three genes (*dnaB*, *recA* and Rv1461) have been invaded by sequences encoding inteins (protein introns) and in all three cases their counterparts in *M. leprae* also contain inteins, but at different sites[15] (S.T.C. *et al.*, unpublished observations).

Protein function, composition and duplication. By using various database comparisons, we attributed precise functions to ~40% of the predicted proteins and found some information or similarity for another 44%. The remaining 16% resembled no known proteins and may account for specific mycobacterial functions. Examination of the amino-acid composition of the *M. tuberculosis* proteome by correspondence analysis[16], and comparison with that of other microorganisms whose genome sequences are available, revealed a statistically significant preference for the amino acids Ala, Gly, Pro, Arg and Trp, which are all encoded by G + C-rich codons, and a comparative reduction in the use of amino acids encoded by A + T-rich codons such as Asn, Ile, Lys, Phe and Tyr (Fig. 3). This approach also identified two groups of proteins rich in Asn or Gly that belong to new families, PE and PPE (see below). The fraction of the proteome that has arisen through gene duplication is similar to that seen in *E. coli* or *B. subtilis* (~51%; refs 9, 14), except that the level of sequence conservation is considerably higher, indicating that there may be extensive redundancy or differential production of the corresponding polypeptides. The apparent lack of divergence following gene duplication is consistent with the hypothesis that *M. tuberculosis* is of recent descent[6].

General metabolism, regulation and drug resistance

Metabolic pathways. From the genome sequence, it is clear that the tubercle bacillus has the potential to synthesize all the essential amino acids, vitamins and enzyme co-factors, although some of the pathways involved may differ from those found in other bacteria. *M. tuberculosis* can metabolize a variety of carbohydrates, hydrocarbons, alcohols, ketones and carboxylic acids[2,17]. It is apparent from genome inspection that, in addition to many functions involved in lipid metabolism, the enzymes necessary for glycolysis, the pentose phosphate pathway, and the tricarboxylic acid and glyoxylate cycles are all present. A large number (~200) of oxidoreductases, oxygenases and dehydrogenases is predicted, as well as many oxygenases containing cytochrome P450, that are similar to fungal proteins involved in sterol degradation. Under aerobic growth conditions, ATP will be generated by oxidative phosphorylation from electron transport chains involving a ubiquinone cytochrome *b* reductase complex and cytochrome *c* oxidase. Components of several anaerobic phosphorylative electron transport chains are also present, including genes for nitrate reductase (*narGHJI*), fumarate reductase (*frdABCD*) and possibly nitrite reductase (*nirBD*), as well as a new reductase (*narX*) that results from a rearrangement of a homologue of the *narGHJI* operon. Two genes encoding haemoglobin-like proteins, which may protect against oxidative stress or be involved in oxygen capture, were found. The ability of the bacillus to adapt its metabolism to environmental change is significant as it not only has to compete with the lung for oxygen but must also adapt to the microaerophilic/anaerobic environment at the heart of the burgeoning granuloma.

Regulation and signal transduction. Given the complexity of the environmental and metabolic choices facing *M. tuberculosis*, an extensive regulatory repertoire was expected. Thirteen putative sigma factors govern gene expression at the level of transcription initiation, and more than 100 regulatory proteins are predicted (Table 1). Unlike *B. subtilis* and *E. coli*, in which there are >30 copies of different two-component regulatory systems[14], *M. tuberculosis* has only 11 complete pairs of sensor histidine kinases and response regulators, and a few isolated kinase and regulatory genes. This relative paucity in environmental signal transduction pathways is probably offset by the presence of a family of eukaryotic-like serine/threonine protein kinases (STPKs), which function as part of a phosphorelay system[18]. The STPKs probably have two domains: the well-conserved kinase domain at the amino terminus is predicted to be connected by a transmembrane segment to the carboxy-terminal region that may respond to specific stimuli. Several of the predicted envelope lipoproteins, such as that encoded by *lppR* (Rv2403), show extensive similarity to this putative receptor domain of STPKs, suggesting possible interplay. The STPKs probably function in signal transduction pathways and may govern important cellular decisions such as dormancy and cell division, and although their partners are unknown, candidate genes for phosphoprotein phosphatases have been identified.

Drug resistance. *M. tuberculosis* is naturally resistant to many antibiotics, making treatment difficult[19]. This resistance is due mainly to the highly hydrophobic cell envelope acting as a permeability barrier[4], but many potential resistance determinants are also encoded in the genome. These include hydrolytic or drug-modifying enzymes such as β-lactamases and aminoglycoside acetyl transferases, and many potential drug–efflux systems, such as 14 members of the major facilitator family and numerous ABC transporters. Knowledge of these putative resistance mechanisms will promote better use of existing drugs and facilitate the conception of new therapies.

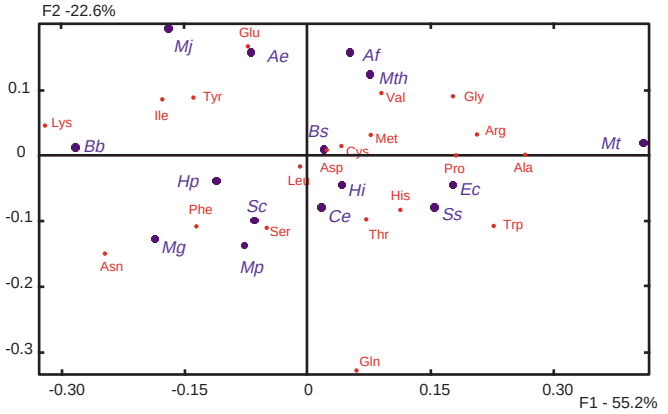
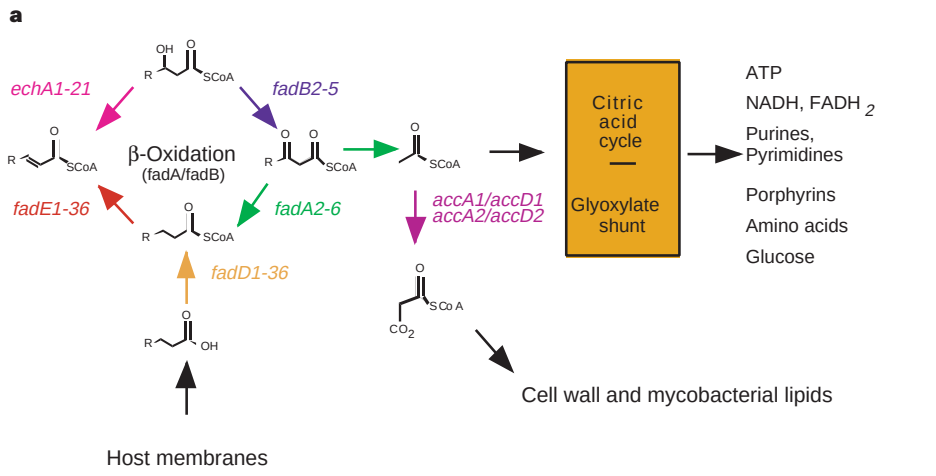
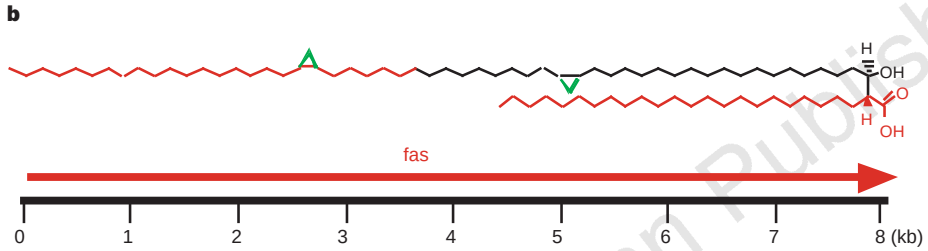


Figure 3 Correspondence analysis of the proteomes from extensively sequenced organisms as a function of amino-acid composition. Note the extreme position of *M. tuberculosis* and the shift in amino-acid preference reflecting increasing G + C content from left to right. Abbreviations used: *Ae*, *Aquifex aeolicus*; *Af*, *Archaeoglobus fulgidis*; *Bb*, *Borrelia burgdorfei*; *Bs*, *B. subtilis*; *Ce*, *Caenorhabditis elegans*; *Ec*, *E. coli*; *Hi*, *Haemophilus influenzae*; *Hp*, *Helicobacter pylori*; *Mg*, *Mycoplasma genitalium*; *Mj*, *Methanococcus jannaschi*; *Mp*, *Mycoplasma pneumoniae*; *Mt*, *M. tuberculosis*; *Mth*, *Methanobacterium thermoautotrophicum*; *Sc*, *Saccharomyces cerevisiae*; *Ss*, *Synechocystis* sp. strain PCC6803. F1 and F2, first and second factorial axes[16].

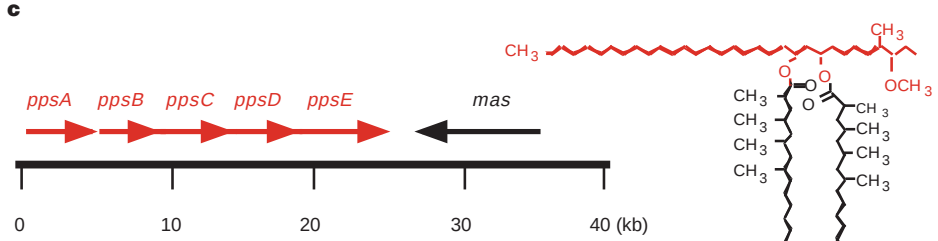
Nature © Macmillan Publishers Ltd 1998

Nature © Macmillan Publishers Ltd 1998





Gene	Function
fas	Fatty acid synthase, produces C_{16}-C_{26} acyl-CoA esters
fabD	Malonyl-CoA:AcpM acyltransferase, AcpM loading
acpM	Acyl carrier protein, meromycolate precursor transport
kasA	Ketoacyl acyl carrier protein synthase, chain elongation
kasB	Ketoacyl acyl carrier protein synthase, chain elongation
accD	Acetyl-CoA carboxylase, malonyl-CoA synthesis
mabA	3-oxo-acyl-acyl carrier protein reductase, reduces KasA/B product
inhA	Enoyl-acyl carrier protein reductase
cmaA1	cyclopropane mycolic acid synthase 1, distal-position specific
cmaA2	cyclopropane mycolic acid synthase 2, proximal-position specific



Gene	Function
mas	Four rounds extension of $C_{16,18}$ using Me-malonyl CoA
ppsA	Extension of C_{18} with malony CoA, partial reduction
ppsB	Extension with malony CoA, partial reduction
ppsC	Extension with malony CoA, complete reduction
ppsD	Extension with Me-malony CoA, partial reduction
ppsE	Extension with malony CoA, partial reduction, decarboxylation

Figure 4 Lipid metabolism. **a**, Degradation of host-cell lipids is vital in the intracellular life of *M. tuberculosis*. Host-cell membranes provide precursors for many metabolic processes, as well as potential precursors of mycobacterial cell-wall constituents, through the actions of a broad family of β-oxidative enzymes encoded by multiple copies in the genome. These enzymes produce acetyl CoA, which can be converted into many different metabolites and fuel for the bacteria through the actions of the enzymes of the citric acid cycle and the glyoxylate shunt of this cycle. **b**, The genes that synthesize mycolic acids, the dominant lipid component of the mycobacterial cell wall, include the type I fatty acid synthase (*fas*) and a unique type II system which relies on extension of a precursor bound to an acyl carrier protein to form full-length (~80-carbon) mycolic acids. The *cma* genes are responsible for cyclopropanation. **c**, The genes that produce phthiocerol dimycocerosate form a large operon and represent type I (*mas*) and type II (the *pps* operon) polyketide synthase systems. Functions are colour coordinated.

Nature © Macmillan Publishers Ltd 1998

Nature © Macmillan Publishers Ltd 1998

Lipid metabolism

Very few organisms produce such a diverse array of lipophilic molecules as *M. tuberculosis*. These molecules range from simple fatty acids such as palmitate and tuberculostearate, through isoprenoids, to very-long-chain, highly complex molecules such as mycolic acids and the phenolphthiocerol alcohols that esterify with mycocerosic acid to form the scaffold for attachment of the mycosides. Mycobacteria contain examples of every known lipid and polyketide biosynthetic system, including enzymes usually found in mammals and plants as well as the common bacterial systems. The biosynthetic capacity is overshadowed by the even more remarkable radiation of degradative, fatty acid oxidation systems and, in total, there are ~250 distinct enzymes involved in fatty acid metabolism in *M. tuberculosis* compared with only 50 in *E. coli*[20].

Fatty acid degradation. *In vivo*-grown mycobacteria have been suggested to be largely lipolytic, rather than lipogenic, because of the variety and quantity of lipids available within mammalian cells and the tubercle[2] (Fig. 4a). The abundance of genes encoding components of fatty acid oxidation systems found by our genomic approach supports this proposition, as there are 36 acyl-CoA synthases and a family of 36 related enzymes that could catalyse the first step in fatty acid degradation. There are 21 homologous enzymes belonging to the enoyl-CoA hydratase/isomerase superfamily of enzymes, which rehydrate the nascent product of the acyl-CoA dehydrogenase. The four enzymes that convert the 3-hydroxy fatty acid into a 3-keto fatty acid appear less numerous, mainly because they are difficult to distinguish from other members of the short-chain alcohol dehydrogenase family on the basis of primary sequence. The five enzymes that complete the cycle by thiolysis of the β-ketoester, the acetyl-CoA C-acetyltransferases, do indeed appear to be a more limited family. In addition to this extensive set of dissociated degradative enzymes, the genome also encodes the canonical FadA/FadB β-oxidation complex (Rv0859 and Rv0860). Accessory activities are present for the metabolism of odd-chain and multiply unsaturated fatty acids.

Fatty acid biosynthesis. At least two discrete types of enzyme system, fatty acid synthase (FAS) I and FAS II, are involved in fatty acid biosynthesis in mycobacteria (Fig. 4b). FAS I (Rv2524, *fas*) is a single polypeptide with multiple catalytic activities that generates several shorter CoA esters from acetyl-CoA primers[5] and probably creates precursors for elongation by all of the other fatty acid and polyketide systems. FAS II consists of dissociable enzyme components which act on a substrate bound to an acyl-carrier protein (ACP). FAS II is incapable of *de novo* fatty acid synthesis but instead elongates palmitoyl-ACP to fatty acids ranging from 24 to 56 carbons in length[17,21]. Several different components of FAS II may be targets for the important tuberculosis drug isoniazid, including the enoyl-ACP reductase InhA[22], the ketoacyl-ACP synthase KasA and the ACP AcpM[21]. Analysis of the genome shows that there are only three potential ketoacyl synthases: KasA and KasB are highly related, and their genes cluster with *acpM*, whereas KasC is a more distant homologue of a ketoacyl synthase III system. The number of ketoacyl synthase and ACP genes indicates that there is a single FAS II system. Its genetic organization, with two clustered ketoacyl synthases, resembles that of type II aromatic polyketide biosynthetic gene clusters, such as those for actinorhodin, tetracycline and tetracenomycin in *Streptomyces* species[23]. InhA seems to be the sole enoyl-ACP reductase and its gene is co-transcribed with a *fabG* homologue, which encodes 3-oxoacyl-ACP reductase. Both of these proteins are probably important in the biosynthesis of mycolic acids.

Fatty acids are synthesized from malonyl-CoA and precursors are generated by the enzymatic carboxylation of acetyl (or propionyl)-CoA by a biotin-dependent carboxylase (Fig. 4b). From study of the genome we predict that there are three complete carboxylase systems, each consisting of an α- and a β-subunit, as well as three β-subunits without an α-counterpart. As a group, all of the carboxylases seem to be more related to the mammalian homologues than to the corresponding bacterial enzymes. Two of these carboxylase systems (*accA1*, *accD1* and *accA2*, *accD2*) are probably involved in degradation of odd-numbered fatty acids, as they are adjacent to genes for other known degradative enzymes. They may convert propionyl-CoA to succinyl-CoA, which can then be incorporated into the tricarboxylic acid cycle. The synthetic carboxylases (*accA3*, *accD3*, *accD4*, *accD5* and *accD6*) are more difficult to understand. The three extra β-subunits might direct carboxylation to the appropriate precursor or may simply increase the total amount of carboxylated precursor available if this step were rate-limiting.

Synthesis of the paraffinic backbone of fatty and mycolic acids in the cell is followed by extensive postsynthetic modifications and unsaturations, particularly in the case of the mycolic acids[24,25]. Unsaturation is catalysed either by a FabA-like β-hydroxyacyl-ACP dehydrase, acting with a specific ketoacyl synthase, or by an aerobic terminal mixed function desaturase that uses both molecular oxygen and NADPH. Inspection of the genome revealed no obvious candidates for the FabA-like activity. However, three potential aerobic desaturases (encoded by *desA1*, *desA2* and *desA3*) were evident that show little similarity to related vertebrate or yeast enzymes (which act on CoA esters) but instead resemble plant desaturases (which use ACP esters). Consequently, the genomic data indicate that unsaturation of the meromycolate chain may occur while the acyl group is bound to AcpM.

Much of the subsequent structural diversity in mycolic acids is generated by a family of *S*-adenosyl-L-methionine-dependent enzymes, which use the unsaturated meromycolic acid as a substrate to generate *cis* and *trans* cyclopropanes and other mycolates. Six members of this family have been identified and characterized[25] and two clustered, convergently transcribed new genes are evident in the genome (*umaA1* and *umaA2*). From the functions of the known family members and the structures of mycolic acids in *M. tuberculosis*, it is tempting to speculate that these new enzymes may introduce the *trans* cyclopropanes into the meromycolate precursor. In addition to these two methyltransferases, there are two other unrelated lipid methyltransferases (Ufa1 and Ufa2) that share homology with cyclopropane fatty acid synthase of *E. coli*[25]. Although cyclopropanation seems to be a relatively common modification of mycolic acids, cyclopropanation of plasma-membrane constituents has not been described in mycobacteria. Tuberculostearic acid is produced by methylation of oleic acid, and may be synthesized by one of these two enzymes.

Condensation of the fully functionalized and preformed meromycolate chain with a 26-carbon α-branch generates full-length mycolic acids that must be transported to their final location for attachment to the cell-wall arabinogalactan. The transfer and subsequent transesterification is mediated by three well-known immunogenic proteins of the antigen 85 complex[26]. The genome encodes a fourth member of this complex, antigen 85C′ (*fbpC2*, Rv0129), which is highly related to antigen 85C. Further studies are needed to show whether the protein possesses mycolytransferase activity and to clarify the reason behind the apparent redundancy.

Polyketide synthesis. Mycobacteria synthesize polyketides by several different mechanisms. A modular type I system, similar to that involved in erythromycin biosynthesis[23], is encoded by a very large operon, *ppsABCDE*, and functions in the production of phenolphthiocerol[5]. The absence of a second type I polyketide synthase suggests that the related lipids phthiocerol A and B, phthiodiolone A and phthiotriol may all be synthesized by the same system, either from alternative primers or by differential postsynthetic modification. It is physiologically significant that the *pps* gene cluster occurs immediately upstream of *mas*, which encodes the multifunctional enzyme mycocerosic acid synthase (MAS), as their products phthiocerol and mycocerosic acid esterify to form the very abundant cell-wall-associated molecule phthiocerol dimycocerosate (Fig. 4c).

Nature © Macmillan Publishers Ltd 1998

Nature © Macmillan Publishers Ltd 1998

Members of another large group of polyketide synthase enzymes are similar to MAS, which also generates the multiply methyl-branched fatty acid components of mycosides and phthiocerol dimycocerosate, abundant cell-wall-associated molecules[5]. Although some of these polyketide synthases may extend type I FAS CoA primers to produce other long-chain methyl-branched fatty acids such as mycolipenic, mycolipodienic and mycolipanolic acids or the phthioceranic and hydroxyphthioceranic acids, or may even show functional overlap[5], there are many more of these enzymes than there are known metabolites. Thus there may be new lipid and polyketide metabolites that are expressed only under certain conditions, such as during infection and disease.

A fourth class of polyketide synthases is related to the plant enzyme superfamily that includes chalcone and stilbene synthase[23]. These polyketide synthases are phylogenetically divergent from all other polyketide and fatty acid synthases and generate unreduced polyketides that are typically associated with anthocyanin pigments and flavonoids. The function of these systems, which are often linked to apparent type I modules, is unknown. An example is the gene cluster spanning *pks10*, *pks7*, *pks8* and *pks9*, which includes two of the chalcone-synthase-like enzymes and two modules of an apparent type I system. The unknown metabolites produced by these enzymes are interesting because of the potent biological activities of some polyketides such as the immunosuppressor rapamycin.

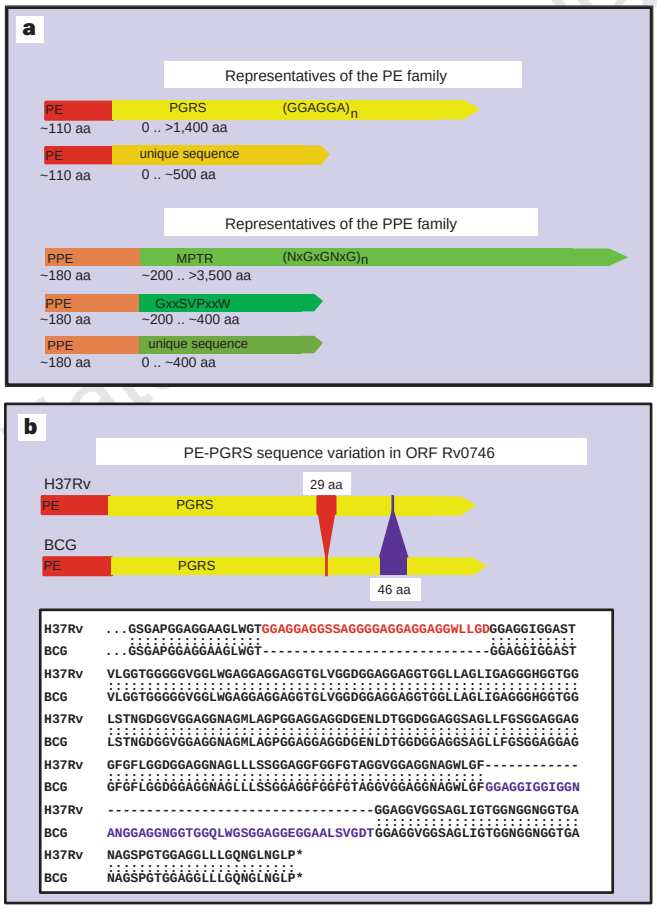


Figure 5 The PE and PPE protein families. **a**, Classification of the PE and PPE protein families. **b**, Sequence variation between *M. tuberculosis* H37Rv and *M. bovis* BCG-Pasteur in the PE-PGRS encoded by open reading frame (ORF) Rv0746.

Siderophores. Peptides that are not ribosomally synthesized are made by a process that is mechanistically analogous to polyketide synthesis[23,27]. These peptides include the structurally related iron-scavenging siderophores, the mycobactins and the exochelins[2,28], which are derived from salicylate by the addition of serine (or threonine), two lysines and various fatty acids and possible polyketide segments. The *mbt* operon, encoding one apparent salicylate-activating protein, three amino-acid ligases, and a single module of a type I polyketide synthase, may be responsible for the biosynthesis of the mycobacterial siderophores. The presence of only one non-ribosomal peptide-synthesis system indicates that this pathway may generate both siderophores and that subsequent modification of a single ε-amino group of one lysine residue may account for the different physical properties and function of the siderophores[28].

Immunological aspects and pathogenicity

Given the scale of the global tuberculosis burden, vaccination is not only a priority but remains the only realistic public health intervention that is likely to affect both the incidence and the prevalence of the disease[29]. Several areas of vaccine development are promising, including DNA vaccination, use of secreted or surface-exposed proteins as immunogens, recombinant forms of BCG and rational attenuation of *M. tuberculosis*[29]. All of these avenues of research will benefit from the genome sequence as its availability will stimulate more focused approaches. Genes encoding ~90 lipoproteins were identified, some of which are enzymes or components of transport systems, and a similar number of genes encoding preproteins (with type I signal peptides) that are probably exported by the Sec-dependent pathway. *M. tuberculosis* seems to have two copies of *secA*. The potent T-cell antigen Esat-6 (ref. 30), which is probably secreted in a Sec-independent manner, is encoded by a member of a multigene family. Examination of the genetic context reveals several similarly organized operons that include genes encoding large ATP-hydrolysing membrane proteins that might act as transporters. One of the surprises of the genome project was the discovery of two extensive families of novel glycine-rich proteins, which may be of immunological significance as they are predicted to be abundant and potentially polymorphic antigens.

The PE and PPE multigene families. About 10% of the coding capacity of the genome is devoted to two large unrelated families of acidic, glycine-rich proteins, the PE and PPE families, whose genes are clustered (Figs 1, 2) and are often based on multiple copies of the polymorphic repetitive sequences referred to as PGRSs, and major polymorphic tandem repeats (MPTRs), respectively[31,32]. The names PE and PPE derive from the motifs Pro–Glu (PE) and Pro–Pro–Glu (PPE) found near the N terminus in most cases[33]. The 99 members of the PE protein family all have a highly conserved N-terminal domain of ~110 amino-acid residues that is predicted to have a globular structure, followed by a C-terminal segment that varies in size, sequence and repeat copy number (Fig. 5). Phylogenetic analysis separated the PE family into several subfamilies. The largest of these is the highly repetitive PGRS class, which contains 61 members; members of the other subfamilies, share very limited sequence similarity in their C-terminal domains (Fig. 5). The predicted molecular weights of the PE proteins vary considerably as a few members contain only the N-terminal domain, whereas most have C-terminal extensions ranging in size from 100 to 1,400 residues. The PGRS proteins have a high glycine content (up to 50%), which is the result of multiple tandem repetitions of Gly–Gly–Ala or Gly–Gly–Asn motifs, or variations thereof.

The 68 members of the PPE protein family (Fig. 5) also have a conserved N-terminal domain that comprises ~180 amino-acid residues, followed by C-terminal segments that vary markedly in sequence and length. These proteins fall into at least three groups, one of which constitutes the MPTR class characterized by the presence of multiple, tandem copies of the motif Asn–X–Gly–X–Gly–Asn–X–Gly. The second subgroup contains a characteristic,

Nature © Macmillan Publishers Ltd 1998

well-conserved motif around position 350, whereas the third contains proteins that are unrelated except for the presence of the common 180-residue PPE domain.

The subcellular location of the PE and PPE proteins is unknown and in only one case, that of a lipase (Rv3097), has a function been demonstrated. On examination of the protein database from the extensively sequenced *M. leprae*[15], no PGRS- or MPTR-related polypeptides were detected but a few proteins belonging to the non-MPTR subgroup of the PPE family were found. These proteins include one of the major antigens recognized by leprosy patients, the serine-rich antigen[34]. Although it is too early to attribute biological functions to the PE and PPE families, it is tempting to speculate that they could be of immunological importance. Two interesting possibilities spring to mind. First, they could represent the principal source of antigenic variation in what is otherwise a genetically and antigenically homogeneous bacterium. Second, these glycine-rich proteins might interfere with immune responses by inhibiting antigen processing.

Several observations and results support the possibility of antigenic variation associated with both the PE and the PPE family proteins. The PGRS member Rv1759 is a fibronectin-binding protein of relative molecular mass 55,000 (ref. 35) that elicits a variable antibody response, indicating either that individuals mount different immune responses or that this PGRS protein may vary between strains of *M. tuberculosis*. The latter possibility is supported by restriction fragment length polymorphisms for various PGRS and MPTR sequences in clinical isolates[33]. Direct support for genetic variation within both the PE and the PPE families was obtained by comparative DNA sequence analysis (Fig. 5). The gene for the PE–PGRS protein Rv0746 of BCG differs from that in H37Rv by the deletion of 29 codons and the insertion of 46 codons. Similar variation was seen in the gene for the PPE protein Rv0442 (data not shown). As these differences were all associated with repetitive sequences they could have resulted from intergenic or intragenic recombinational events or, more probably, from strand slippage during replication[32]. These mechanisms are known to generate antigenic variability in other bacterial pathogens[36].

There are several parallels between the PGRS proteins and the Epstein–Barr virus nuclear antigens (EBNAs). Members of both polypeptide families are glycine-rich, contain extensive Gly–Ala repeats, and exhibit variation in the length of the repeat region between different isolates. The Gly–Ala repeat region of EBNA1 functions as a *cis*-acting inhibitor of the ubiquitin/proteasome antigen-processing pathway that generates peptides presented in the context of major histocompatibility complex (MHC) class I molecules[37,38]. MHC class I knockout mice are very susceptible to *M. tuberculosis*, underlining the importance of a cytotoxic T-cell response in protection against disease[3,39]. Given the many potential effects of the PPE and PE proteins, it is important that further studies are performed to understand their activity. If extensive antigenic variability or reduced antigen presentation were indeed found, this would be significant for vaccine design and for understanding protective immunity in tuberculosis, and might even explain the varied responses seen in different BCG vaccination programmes[40].

Pathogenicity. Despite intensive research efforts, there is little information about the molecular basis of mycobacterial virulence[41]. However, this situation should now change as the genome sequence will accelerate the study of pathogenesis as never before, because other bacterial factors that may contribute to virulence are becoming apparent. Before the completion of the genome sequence, only three virulence factors had been described[41]: catalase-peroxidase, which protects against reactive oxygen species produced by the phagocyte; *mce*, which encodes macrophage-colonizing factor[42]; and a sigma factor gene, *sigA* (aka *rpoV*), mutations in which can lead to attenuation[41]. In addition to these single-gene virulence factors, the mycobacterial cell wall[4] is also important in pathology, but the complex nature of its biosynthesis makes it difficult to identify critical genes whose inactivation would lead to attenuation.

On inspection of the genome sequence, it was apparent that four copies of *mce* were present and that these were all situated in operons, comprising eight genes, organized in exactly the same manner. In each case, the genes preceding *mce* code for integral membrane proteins, whereas *mce* and the following five genes are all predicted to encode proteins with signal sequences or hydrophobic stretches at the N terminus. These sets of proteins, about which little is known, may well be secreted or surface-exposed; this is consistent with the proposed role of Mce in invasion of host cells[42]. Furthermore, a homologue of *smpB*, which has been implicated in intracellular survival of *Salmonella typhimurium*, has also been identified[43]. Among the other secreted proteins identified from the genome sequence that could act as virulence factors are a series of phospholipases C, lipases and esterases, which might attack cellular or vacuolar membranes, as well as several proteases. One of these phospholipases acts as a contact-dependent haemolysin (N. Stoker, personal communication). The presence of storage proteins in the bacillus, such as the haemoglobin-like oxygen captors described above, points to its ability to stockpile essential growth factors, allowing it to persist in the nutrient-limited environment of the phagosome. In this regard, the ferritin-like proteins, encoded by *bfrA* and *bfrB*, may be important in intracellular survival as the capacity to acquire enough iron in the vacuole is very limited. □

Methods

Sequence analysis. Initially, ~3.2 Mb of sequence was generated from cosmids[8] and the remainder was obtained from selected BAC clones[7] and 45,000 whole-genome shotgun clones. Sheared fragments (1.4–2.0 kb) from cosmids and BACs were cloned into M13 vectors, whereas genomic DNA was cloned in pUC18 to obtain both forward and reverse reads. The PGRS genes were grossly underrepresented in pUC18 but better covered in the BAC and cosmid M13 libraries. We used small-insert libraries[44] to sequence regions prone to compression or deletion and, in some cases, obtained sequences from products of the polymerase chain reaction or directly from BACs[7]. All shotgun sequencing was performed with standard dye terminators to minimize compression problems, whereas finishing reactions used dRhodamine or BigDye terminators (http://www.sanger.ac.uk). Problem areas were verified by using dye primers. Thirty differences were found between the genomic shotgun sequences and the cosmids; twenty of which were due to sequencing errors and ten to mutations in cosmids (1 error per 320 kb). Less than 0.1% of the sequence was from areas of single-clone coverage, and <0.2% was from one strand with only one sequencing chemistry.

Informatics. Sequence assembly involved PHRAP, GAP4 (ref. 45) and a customized perl script that merges sequences from different libraries and generates segments that can be processed by several finishers simultaneously. Sequence analysis and annotation was managed by DIANA (B.G.B. *et al.*, unpublished). Genes encoding proteins were identified by TB-parse[46] using a hidden Markov model trained on known *M. tuberculosis* coding and non-coding regions and translation-initiation signals, with corroboration by positional base preference. Interrogation of the EMBL, TREMBL, SwissProt, PROSITE[47] and in-house databases involved BLASTN, BLASTX[48], DOTTER (http://www.sanger.ac.uk) and FASTA[49]. tRNA genes were located and identified using tRNAscan and tRNAscan-SE[50]. The complete sequence, a list of annotated cosmids and linking regions can be found on our website (http://www. sanger.ac.uk) and in MycDB (http://www.pasteur.fr/mycdb/).

Received 15 April; accepted 8 May 1998.

1. Snider, D. E. Jr, Raviglione, M. & Kochi, A. in *Tuberculosis: Pathogenesis, Protection, and Control* (ed. Bloom, B. R.) 2–11 (Am. Soc. Microbiol., Washington DC, 1994).
2. Wheeler, P. R. & Ratledge, C. in *Tuberculosis: Pathogenesis, Protection, and Control* (ed. Bloom, B. R.) 353–385 (Am. Soc. Microbiol., Washington DC, 1994).
3. Chan, J. & Kaufmann, S. H. E. in *Tuberculosis: Pathogenesis, Protection, and Control* (ed. Bloom, B. R.) 271–284 (Am. Soc. Microbiol., Washington DC, 1994).
4. Brennan, P. J. & Draper, P. in *Tuberculosis: Pathogenesis, Protection, and Control* (ed. Bloom, B. R.) 271–284 (Am. Soc. Microbiol., Washington DC, 1994).

© Nature Publishing Group 1998

Nature © Macmillan Publishers Ltd 1998

5. Kolattukudy, P. E., Fernandes, N. D., Azad, A. K., Fitzmaurice, A. M. & Sirakova, T. D. Biochemistry and molecular genetics of cell-wall lipid biosynthesis in mycobacteria. *Mol. Microbiol.* **24,** 263–270 (1997).
6. Sreevatsan, S. *et al*. Restricted structural gene polymorphism in the *Mycobacterium tuberculosis* complex indicates evolutionarily recent global dissemination. *Proc. Natl Acad. Sci. USA* **94,** 9869–9874 (1997).
7. Brosch, R. *et al*. Use of a *Mycobacterium tuberculosis* H37Rv bacterial artificial chromosome library for genome mapping, sequencing and comparative genomics. *Infect. Immun.* **66,** 2221–2229 (1998).
8. Philipp, W. J. *et al*. An integrated map of the genome of the tubercle bacillus, *Mycobacterium tuberculosis* H37Rv, and comparison with *Mycobacterium leprae*. *Proc. Natl Acad. Sci. USA* **93,** 3132–3137 (1996).
9. Blattner, F. R. *et al*. The complete genome sequence of *Escherichia coli* K-12. *Science* **277,** 1453–1462 (1997).
10. Cole, S. T. & Saint-Girons, I. Bacterial genomics. *FEMS Microbiol. Rev.* **14,** 139–160 (1994).
11. Freiberg, C. *et al*. Molecular basis of symbiosis between *Rhizobium* and legumes. *Nature* **387,** 394–401 (1997).
12. Bardarov, S. *et al*. Conditionally replicating mycobacteriophages: a system for transposon delivery to *Mycobacterium tuberculosis*. *Proc. Natl Acad. Sci. USA* **94,** 10961–10966 (1997).
13. Mahairas, G. G., Sabo, P. J., Hickey, M. J., Singh, D. C. & Stover, C. K. Molecular analysis of genetic differences between *Mycobacterium bovis* BCG and virulent *M. bovis*. *J. Bacteriol.* **178,** 1274–1282 (1996).
14. Kunst, F. *et al*. The complete genome sequence of the gram-positive bacterium *Bacillus subtilis*. *Nature* **390,** 249–256 (1997).
15. Smith, D. R. *et al*. Multiplex sequencing of 1.5 Mb of the *Mycobacterium leprae* genome. *Genome Res.* **7,** 802–819 (1997).
16. Greenacre, M. *Theory and Application of Correspondence Analysis* (Academic, London, 1984).
17. Ratledge, C. R. in *The Biology of the Mycobacteria* (eds Ratledge, C. & Stanford, J.) 53–94 (Academic, San Diego, 1982).
18. Av-Gay, Y. & Davies, J. Components of eukaryotic-like protein signaling pathways in *Mycobacterium tuberculosis*. *Microb. Comp. Genomics* **2,** 63–73 (1997).
19. Cole, S. T. & Telenti, A. Drug resistance in *Mycobacterium tuberculosis*. *Eur. Resp. Rev.* **8,** 701S–713S (1995).
20. Riley, M. & Labedan, B. in Escherichia coli *and* Salmonella (ed. Neidhardt, F. C.) 2118–2202 (ASM, Washington, 1996).
21. Mdluli, K. *et al*. Inhibition of a *Mycobacterium tuberculosis* β-ketoacyl ACP synthase by isoniazid. *Science* **280,** 1607–1610 (1998).
22. Banerjee, A. *et al*. *inhA*, a gene encoding a target for isoniazid and ethionamide in *Mycobacterium tuberculosis*. *Science* **263,** 227–230 (1994).
23. Hopwood, D. A. Genetic contributions to understanding polyketide synthases. *Chem. Rev.* **97,** 2465–2497 (1997).
24. Minnikin, D. E. in *The Biology of the Mycobacteria* (eds Ratledge, C. & Stanford, J.) 95–184 (Academic, London, 1982).
25. Barry, C. E. III *et al*. Mycolic acids: structure, biosynthesis, and phsyiological functions. *Prog. Lipid Res.* (in the press).
26. Belisle, J. T. *et al*. Role of the major antigen of *Mycobacterium tuberculosis* in cell wall biogenesis. *Science* **276,** 1420–1422 (1997).
27. Marahiel, M. A., Stachelhaus, T. & Mootz, H. D. Modular peptide synthetases involved in nonribosomal peptide synthesis. *Chem. Rev.* **97,** 2651–2673 (1997).
28. Gobin, J. *et al*. Iron acquisition by *Mycobacterium tuberculosis*: isolation and characterization of a family of iron-binding exochelins. *Proc. Natl Acad. Sci. USA* **92,** 5189–5193 (1995).
29. Young, D. B. & Fruth, U. in *New Generation Vaccines* (eds Levine, M., Woodrow, G., Kaper, J. & Cobon, G. S.) 631–645 (Marcel Dekker, New York, 1997).
30. Sorensen, A. L., Nagai, S., Houen, G., Andersen, P. & Anderson, A. B. Purification and characterization of a low-molecular-mass T-cell antigen secreted by *Mycobacterium tuberculosis*. *Infect. Immun.* **63,** 1710–1717 (1995).
31. Hermans, P. W. M., van Soolingen, D. & van Embden, J. D. A. Characterization of a major polymorphic tandem repeat in *Mycobacterium tuberculosis* and its potential use in the epidemiology of *Mycobacterium kansasii* and *Mycobacterium gordonae*. *J. Bacteriol.* **174,** 4157–4165 (1992).
32. Poulet, S. & Cole, S. T. Characterisation of the polymorphic GC-rich repetitive sequence (PGRS) present in *Mycobacterium tuberculosis*. *Arch. Microbiol.* **163,** 87–95 (1995).
33. Cole, S. T. & Barrell, B. G. in *Genetics and Tuberculosis* (eds Chadwick, D. J. & Cardew, G., *Novartis Foundation Symp. 217*) 160–172 (Wiley, Chichester, 1998).
34. Vega-Lopez, F. *et al*. Sequence and immunological characterization of a serine-rich antigen from *Mycobacterium leprae*. *Infect. Immun.* **61,** 2145–2153 (1993).
35. Abou-Zeid, C. *et al*. Genetic and immunological analysis of *Mycobacterium tuberculosis* fibronectin-binding proteins. *Infect. Immun.* **59,** 2712–2718 (1991).
36. Robertson, B. D. & Meyer, T. F. Genetic variation in pathogenic bacteria. *Trends Genet.* **8,** 422–427 (1992).
37. Levitskaya, J. *et al*. Inhibition of antigen processing by the internal repeat region of the Epstein-Barr virus nuclear antigen-1. *Nature* **375,** 685–688 (1995).
38. Levitskaya, J., Sharipo, A., Leonchiks, A., Ciechanover, A. & Masucci, M. G. Inhibition of ubiquitin/proteasome-dependent protein degradation by the Gly-Ala repeat domain of the Epstein-Barr virus nuclear antigen 1. *Proc. Natl Acad. Sci. USA* **94,** 12616–12621 (1997).
39. Flynn, J. L., Goldstein, M. A., Treibold, K. J., Koller, B. & Bloom, B. R. Major histocompatability complex class-I restricted T cells are required for resistance to *Mycobacterium tuberculosis* infection. *Proc. Natl Acad. Sci. USA* **89,** 12013–12017 (1992).
40. Bloom, B. R. & Fine, P. E. M. in *Tuberculosis: Pathogenesis, Protection, and Control* (ed. Bloom, B. R.) 531–557 (Am. Soc. Microbiol., Washington DC, 1994).
41. Collins, D. M. In search of tuberculosis virulence genes. *Trends Microbiol.* **4,** 426–430 (1996).
42. Arruda, S., Bomfim, G., Knights, R., Huima-Byron, T. & Riley, L. W. Cloning of an *M. tuberculosis* DNA fragment associated with entry and survival inside cells. *Science* **261,** 1454–1457 (1993).
43. Baumler, A. J., Kusters, J. G., Stojikovic, I. & Heffron, F. *Salmonella typhimurium* loci involved in survival within macrophages. *Infect. Immun.* **62,** 1623–1630 (1994).
44. McMurray, A. A., Sulston, J. E. & Quail, M. A. Short-insert libraries as a method of problem solving in genome sequencing. *Genome Res.* **8,** 562–566 (1998).
45. Bonfield, J. K., Smith, K. F. & Staden, R. A new DNA sequence assembly program. *Nucleic Acids Res.* **24,** 4992–4999 (1995).
46. Krogh, A., Mian, I. S. & Haussler, D. A hidden Markov model that finds genes in *E. coli* DNA. *Nucleic Acids Res.* **22,** 4768–4778 (1994).
47. Bairoch, A., Bucher, P. & Hofmann, K. The PROSITE database, its status in 1997. *Nucleic Acids Res.* **25,** 217–221 (1997).
48. Altschul, S., Gish, W., Miller, W., Myers, E. & Lipman, D. A basic local alignment search tool. *J. Mol. Biol.* **215,** 403–410 (1990).
49. Pearson, W. & Lipman, D. Improved tools for biological sequence comparisons. *Proc. Natl Acad. USA* **85,** 2444–2448 (1988).
50. Lowe, T. M. & Eddy, S. R. tRNAscan-SE: a program for improved detection of transfer RNA genes in genomic DNA. *Nucleic Acids Res.* **25,** 955–964 (1997).

Acknowledgements. We thank Y. Av-Gay, F.-C. Bange, A. Danchin, B. Dujon, W. R. Jacobs Jr, L. Jones, M. McNeil, I. Moszer, P. Rice and J. Stephenson for advice, reagents and support. This work was supported by the Wellcome Trust. Additional funding was provided by the Association Française Raoul Follereau, the World Health Organisation and the Institut Pasteur. S.V.G. received a Wellcome Trust travelling research fellowship.

Correspondence and requests for materials should be addressed to B.G.B. (barrell@sanger.ac.uk) or S.T.C. (stcole@pasteur.fr). The complete sequence has been deposited in EMBL/GenBank/DDBJ as MTBH37RV, accession number AL123456.

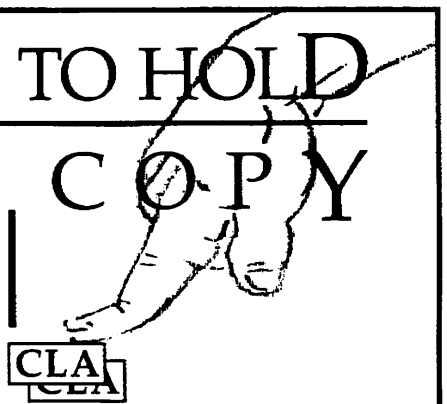
YOURS TO HAVE AND TO HOLD
BUT NOT TO COPY

The publication you are reading is protected by copyright law.

Photocopying copyright material without permission is no different from stealing a magazine from a newsagent, only it doesn't seem like theft.

If you take photocopies from books, magazines and periodicals at work your employer should be licensed with CLA.

Make sure you are protected by a photocopying licence.



The Copyright Licensing Agency Limited
90 Tottenham Court Road, London W1P 0LP
Telephone: 0171 436 5931 Fax: 0171 436 3986

Nature © Macmillan Publishers Ltd 1998

Table 1. Functional classification of *Mycobacterium tuberculosis* protein-coding genes

I. Small-molecule metabolism

A. Degradation

1. Carbon compounds

Rv0186	*bglS*	-glucosidase
Rv2202c	*cbhK*	carbohydrate kinase
Rv0727c	*fucA*	L-fuculose phosphate aldolase
Rv1731	*gabD1*	succinate-semialdehyde dehydrogenase
Rv0234c	*gabD2*	succinate-semialdehyde dehydrogenase
Rv0501	*galE1*	UDP-glucose 4-epimerase
Rv0536	*galE2*	UDP-glucose 4-epimerase
Rv0620	*galK*	galactokinase
Rv0619	*galT*	galactose-1-phosphate uridylyltransferase C-term
Rv0618	*galT'*	galactose-1-phosphate uridylyltransferase N-term
Rv0993	*galU*	UTP-glucose-1-phosphate uridylyltransferase
Rv3696c	*glpK*	ATP:glycerol 3-phosphotransferase
Rv3255c	*manA*	mannose-6-phosphate isomerase
Rv3441c	*mrsA*	phosphoglucomutase or phosphomannomutase
Rv0118c	*oxcA*	oxalyl-CoA decarboxylase
Rv3068c	*pgmA*	phosphoglucomutase
Rv3257c	*pmmA*	phosphomannomutase
Rv3308	*pmmB*	phosphomannomutase
Rv2702	*ppgK*	polyphosphate glucokinase
Rv0408	*pta*	phosphate acetyltransferase
Rv0729	*xylB*	xylulose kinase
Rv1096	-	carbohydrate degrading enzyme

2. Amino acids and amines

Rv1905c	*aao*	D-amino acid oxidase
Rv2531c	*adi*	ornithine/arginine decarboxylase
Rv2780	*ald*	L-alanine dehydrogenase
Rv1538c	*ansA*	L-asparaginase
Rv1001	*arcA*	arginine deiminase
Rv0753c	*mmsA*	methylmalmonate semialdehyde dehydrogenase
Rv0751c	*mmsB*	methylmalmonate semialdehyde oxidoreductase
Rv1187	*rocA*	pyrroline-5-carboxylate dehydrogenase
Rv2322c	*rocD1*	ornithine aminotransferase
Rv2321c	*rocD2*	ornithine aminotransferase
Rv1848	*ureA*	urease subunit
Rv1849	*ureB*	urease subunit
Rv1850	*ureC*	urease subunit
Rv1853	*ureD*	urease accessory protein
Rv1851	*ureF*	urease accessory protein
Rv1852	*ureG*	urease accessory protein
Rv2913c	-	probable D-amino acid aminohydrolase
Rv3551	-	possible glutaconate CoA-transferase

3. Fatty acids

Rv2501c	*accA1*	acetyl/propionyl-CoA carboxylase, subunit
Rv0973c	*accA2*	acetyl/propionyl-CoA carboxylase, subunit
Rv2502c	*accD1*	acetyl/propionyl-CoA carboxylase, subunit
Rv0974c	*accD2*	acetyl/propionyl-CoA carboxylase, subunit
Rv3667	*acs*	acetyl-CoA synthase
Rv3409c	*choD*	cholesterol oxidase
Rv0222	*echA1*	enoyl-CoA hydratase/isomerase superfamily
Rv0456c	*echA2*	enoyl-CoA hydratase/isomerase superfamily
Rv0632c	*echA3*	enoyl-CoA hydratase/isomerase superfamily
Rv0673	*echA4*	enoyl-CoA hydratase/isomerase superfamily
Rv0675	*echA5*	enoyl-CoA hydratase/isomerase superfamily
Rv0905	*echA6*	enoyl-CoA hydratase/isomerase superfamily (aka *eccH*)
Rv0971c	*echA7*	enoyl-CoA hydratase/isomerase superfamily
Rv1070c	*echA8*	enoyl-CoA hydratase/isomerase superfamily
Rv1071c	*echA9*	enoyl-CoA hydratase/isomerase superfamily
Rv1142c	*echA10*	enoyl-CoA hydratase/isomerase superfamily
Rv1141c	*echA11*	enoyl-CoA hydratase/isomerase superfamily
Rv1472	*echA12*	enoyl-CoA hydratase/isomerase superfamily
Rv1935c	*echA13*	enoyl-CoA hydratase/isomerase superfamily
Rv2486	*echA14*	enoyl-CoA hydratase/isomerase superfamily
Rv2679	*echA15*	enoyl-CoA hydratase/isomerase superfamily
Rv2831	*echA16*	enoyl-CoA hydratase/isomerase superfamily
Rv3039c	*echA17*	enoyl-CoA hydratase/isomerase superfamily
Rv3373	*echA18*	enoyl-CoA hydratase/isomerase superfamily, N-term
Rv3374	*echA18'*	enoyl-CoA hydratase/isomerase superfamily, C-term
Rv3516	*echA19*	enoyl-CoA hydratase/isomerase superfamily
Rv3550	*echA20*	enoyl-CoA hydratase/isomerase superfamily
Rv3774	*echA21*	enoyl-CoA hydratase/isomerase superfamily
Rv0859	*fadA*	oxidation complex, subunit (acetyl-CoA C-acetyltransferase)
Rv0243	*fadA2*	acetyl-CoA C-acetyltransferase
Rv1074c	*fadA3*	acetyl-CoA C-acetyltransferase
Rv1323	*fadA4*	acetyl-CoA C-acetyltransferase (aka *thiL*)
Rv3546	*fadA5*	acetyl-CoA C-acetyltransferase
Rv3556c	*fadA6*	acetyl-CoA C-acetyltransferase
Rv0860	*fadB*	oxidation complex, subunit (multiple activities)
Rv0468	*fadB2*	3-hydroxyacyl-CoA dehydrogenase
Rv1715	*fadB3*	3-hydroxyacyl-CoA dehydrogenase
Rv3141	*fadB4*	3-hydroxyacyl-CoA dehydrogenase
Rv1912c	*fadB5*	3-hydroxyacyl-CoA dehydrogenase
Rv1750c	*fadD1*	acyl-CoA synthase
Rv0270	*fadD2*	acyl-CoA synthase
Rv3561	*fadD3*	acyl-CoA synthase
Rv0214	*fadD4*	acyl-CoA synthase
Rv0166	*fadD5*	acyl-CoA synthase
Rv1206	*fadD6*	acyl-CoA synthase
Rv0119	*fadD7*	acyl-CoA synthase
Rv0551c	*fadD8*	acyl-CoA synthase
Rv2590	*fadD9*	acyl-CoA synthase
Rv0099	*fadD10*	acyl-CoA synthase
Rv1550	*fadD11*	acyl-CoA synthase, N-term
Rv1549	*fadD11'*	acyl-CoA synthase, C-term
Rv1427c	*fadD12*	acyl-CoA synthase
Rv3089	*fadD13*	acyl-CoA synthase
Rv1058	*fadD14*	acyl-CoA synthase
Rv2187	*fadD15*	acyl-CoA synthase
Rv0852	*fadD16*	acyl-CoA synthase
Rv3506	*fadD17*	acyl-CoA synthase
Rv3513c	*fadD18*	acyl-CoA synthase
Rv3515c	*fadD19*	acyl-CoA synthase
Rv1185c	*fadD21*	acyl-CoA synthase
Rv2948c	*fadD22*	acyl-CoA synthase
Rv3826	*fadD23*	acyl-CoA synthase
Rv1529	*fadD24*	acyl-CoA synthase
Rv1521	*fadD25*	acyl-CoA synthase
Rv2930	*fadD26*	acyl-CoA synthase
Rv0275c	*fadD27*	acyl-CoA synthase
Rv2941	*fadD28*	acyl-CoA synthase
Rv2950c	*fadD29*	acyl-CoA synthase
Rv0404	*fadD30*	acyl-CoA synthase
Rv1925	*fadD31*	acyl-CoA synthase
Rv3801c	*fadD32*	acyl-CoA synthase
Rv1345	*fadD33*	acyl-CoA synthase
Rv0035	*fadD34*	acyl-CoA synthase
Rv2505c	*fadD35*	acyl-CoA synthase
Rv1193	*fadD36*	acyl-CoA synthase
Rv0131c	*fadE1*	acyl-CoA dehydrogenase
Rv0154c	*fadE2*	acyl-CoA dehydrogenase
Rv0215c	*fadE3*	acyl-CoA dehydrogenase
Rv0231	*fadE4*	acyl-CoA dehydrogenase
Rv0244c	*fadE5*	acyl-CoA dehydrogenase
Rv0271c	*fadE6*	acyl-CoA dehydrogenase
Rv0400c	*fadE7*	acyl-CoA dehydrogenase
Rv0672	*fadE8*	acyl-CoA dehydrogenase (aka *aidB*)
Rv0752c	*fadE9*	acyl-CoA dehydrogenase
Rv0873	*fadE10*	acyl-CoA dehydrogenase
Rv0972c	*fadE12*	acyl-CoA dehydrogenase
Rv0975c	*fadE13*	acyl-CoA dehydrogenase
Rv1346	*fadE14*	acyl-CoA dehydrogenase
Rv1467c	*fadE15*	acyl-CoA dehydrogenase
Rv1679	*fadE16*	acyl-CoA dehydrogenase
Rv1934c	*fadE17*	acyl-CoA dehydrogenase
Rv1933c	*fadE18*	acyl-CoA dehydrogenase
Rv2500c	*fadE19*	acyl-CoA dehydrogenase (aka *mmgC*)
Rv2724c	*fadE20*	acyl-CoA dehydrogenase
Rv2789c	*fadE21*	acyl-CoA dehydrogenase
Rv3061c	*fadE22*	acyl-CoA dehydrogenase
Rv3140	*fadE23*	acyl-CoA dehydrogenase
Rv3139	*fadE24*	acyl-CoA dehydrogenase
Rv3274c	*fadE25*	acyl-CoA dehydrogenase
Rv3504	*fadE26*	acyl-CoA dehydrogenase
Rv3505	*fadE27*	acyl-CoA dehydrogenase
Rv3544c	*fadE28*	acyl-CoA dehydrogenase
Rv3543c	*fadE29*	acyl-CoA dehydrogenase
Rv3560c	*fadE30*	acyl-CoA dehydrogenase
Rv3562	*fadE31*	acyl-CoA dehydrogenase
Rv3563	*fadE32*	acyl-CoA dehydrogenase
Rv3564	*fadE33*	acyl-CoA dehydrogenase
Rv3573c	*fadE34*	acyl-CoA dehydrogenase
Rv3797	*fadE35*	acyl-CoA dehydrogenase
Rv3761c	*fadE36*	acyl-CoA dehydrogenase
Rv1175c	*fadH*	2,4-Dienoyl-CoA Reductase
Rv0855	*far*	fatty acyl-CoA racemase
Rv1143	*mcr*	-methyl acyl-CoA racemase
Rv1492	*mutA*	methylmalonyl-CoA mutase, subunit
Rv1493	*mutB*	methylmalonyl-CoA mutase, subunit
Rv2504c	*scoA*	3-oxo acid:CoA transferase, subunit
Rv2503c	*scoB*	3-oxo acid:CoA transferase, subunit
Rv1136	-	probable carnitine racemase
Rv1683	-	possible acyl-CoA synthase

4. Phosphorous compounds

Rv2368c	*phoH*	ATP-binding *pho* regulon component
Rv1095	*phoH2*	PhoH-like protein
Rv3628	*ppa*	probable inorganic pyrophosphatase
Rv2984	*ppk*	polyphosphate kinase

B. Energy metabolism

1. Glycolysis

Rv1023	*eno*	enolase
Rv0363c	*fba*	fructose bisphosphate aldolase
Rv1436	*gap*	glyceraldehyde 3-phosphate dehydrogenase
Rv0489	*gpm*	phosphoglycerate mutase I
Rv3010c	*pfkA*	phosphofructokinase I
Rv2029c	*pfkB*	phosphofructokinase II
Rv0946c	*pgi*	glucose-6-phosphate isomerase
Rv1437	*pgk*	phosphoglycerate kinase
Rv1617	*pykA*	pyruvate kinase
Rv1438	*tpi*	triosephosphate isomerase
Rv2419c	-	putative phosphoglycerate mutase
Rv3837c	-	putative phosphoglycerate mutase

2. Pyruvate dehydrogenase

Rv2241	*aceE*	pyruvate dehydrogenase E1 component
Rv3303c	*lpdA*	dihydrolipoamide dehydrogenase
Rv2497c	*pdhA*	pyruvate dehydrogenase E1 component subunit
Rv2496c	*pdhB*	pyruvate dehydrogenase E1 component subunit
Rv2495c	*pdhC*	dihydrolipoamide acetyltransferase
Rv0462	-	probable dihydrolipoamide dehydrogenase

3. TCA cycle

Rv1475c	*acn*	aconitate hydratase
Rv0889c	*citA*	citrate synthase 2
Rv2498c	*citE*	citrate lyase chain
Rv1098c	*fum*	fumarase
Rv1131	*gltA1*	citrate synthase 3
Rv0896	*gltA2*	citrate synthase 1
Rv3339c	*icd1*	isocitrate dehydrogenase
Rv0066c	*icd2*	isocitrate dehydrogenase
Rv0794c	*lpdB*	dihydrolipoamide dehydrogenase
Rv1240	*mdh*	malate dehydrogenase
Rv2967c	*pca*	pyruvate carboxylase
Rv3318	*sdhA*	succinate dehydrogenase A
Rv3319	*sdhB*	succinate dehydrogenase B
Rv3316	*sdhC*	succinate dehydrogenase C subunit
Rv3317	*sdhD*	succinate dehydrogenase D subunit
Rv1248c	*sucA*	2-oxoglutarate dehydrogenase
Rv2215	*sucB*	dihydrolipoamide succinyltransferase
Rv0951	*sucC*	succinyl-CoA synthase chain
Rv0952	*sucD*	succinyl-CoA synthase chain

4. Glyoxylate bypass

Rv0467	*aceA*	isocitrate lyase
Rv1915	*aceAa*	isocitrate lyase, module
Rv1916	*aceAb*	isocitrate lyase, module
Rv1837c	*glcB*	malate synthase
Rv3323c	*gphA*	phosphoglycolate phosphatase

5. Pentose phosphate pathway

Rv1445c	*devB*	glucose-6-phosphate 1-dehydrogenase
Rv1844c	*gnd*	6-phosphogluconate dehydrogenase (Gram –)
Rv1122	*gnd2*	6-phosphogluconate dehydrogenase (Gram +)
Rv1446c	*opcA*	unknown function, may aid G6PDH

Nature © Macmillan Publishers Ltd 1998

Nature © Macmillan Publishers Ltd 1998

Rv2436	*rbsK*	ribokinase
Rv1408	*rpe*	ribulose-phosphate 3-epimerase
Rv2465c	*rpi*	phosphopentose isomerase
Rv1448c	*tal*	transaldolase
Rv1449c	*tkt*	transketolase
Rv1121	*zwf*	glucose-6-phosphate 1-dehydrogenase
Rv1447c	*zwf2*	glucose-6-phosphate 1-dehydrogenase

6. Respiration

a. aerobic

Rv0527	*ccsA*	cytochrome *c*-type biogenesis protein
Rv0529	*ccsB*	cytochrome *c*-type biogenesis protein
Rv1451	*ctaB*	cytochrome *c* oxidase assembly factor
Rv2200c	*ctaC*	cytochrome *c* oxidase chain II
Rv3043c	*ctaD*	cytochrome *c* oxidase polypeptide I
Rv2193	*ctaE*	cytochrome *c* oxidase polypeptide III
Rv1542c	*glbN*	hemoglobin-like, oxygen carrier
Rv2470	*glbO*	hemoglobin-like, oxygen carrier
Rv2249c	*glpD1*	glycerol-3-phosphate dehydrogenase
Rv3302c	*glpD2*	glycerol-3-phosphate dehydrogenase
Rv0694	*lldD1*	L-lactate dehydrogenase (cytochrome)
Rv1872c	*lldD2*	L-lactate dehydrogenase
Rv1854c	*ndh*	probable NADH dehydrogenase
Rv3145	*nuoA*	NADH dehydrogenase chain A
Rv3146	*nuoB*	NADH dehydrogenase chain B
Rv3147	*nuoC*	NADH dehydrogenase chain C
Rv3148	*nuoD*	NADH dehydrogenase chain D
Rv3149	*nuoE*	NADH dehydrogenase chain E
Rv3150	*nuoF*	NADH dehydrogenase chain F
Rv3151	*nuoG*	NADH dehydrogenase chain G
Rv3152	*nuoH*	NADH dehydrogenase chain H
Rv3153	*nuoI*	NADH dehydrogenase chain I
Rv3154	*nuoJ*	NADH dehydrogenase chain J
Rv3155	*nuoK*	NADH dehydrogenase chain K
Rv3156	*nuoL*	NADH dehydrogenase chain L
Rv3157	*nuoM*	NADH dehydrogenase chain M
Rv3158	*nuoN*	NADH dehydrogenase chain N
Rv2195	*qcrA*	Rieske iron-sulphur component of *ubiQ-cytB* reductase
Rv2196	*qcrB*	cytochrome component of *ubiQ-cytB* reductase
Rv2194	*qcrC*	cytochrome *b/c* component of *ubiQ-cytB* reductase

b. anaerobic

Rv2392	*cysH*	3'-phosphoadenylylsulfate (PAPS) reductase
Rv2899c	*fdhD*	affects formate dehydrogenase-N
Rv2900c	*fdhF*	molybdopterin-containing oxidoreductase
Rv1552	*frdA*	fumarate reductase flavoprotein subunit
Rv1553	*frdB*	fumarate reductase iron sulphur protein
Rv1554	*frdC*	fumarate reductase 15kD anchor protein
Rv1555	*frdD*	fumarate reductase 13kD anchor protein
Rv1161	*narG*	nitrate reductase subunit
Rv1162	*narH*	nitrate reductase chain
Rv1164	*narI*	nitrate reductase chain
Rv1163	*narJ*	nitrate reductase chain
Rv1736c	*narX*	fused nitrate reductase
Rv2391	*nirA*	probable nitrite reductase/sulphite reductase
Rv0252	*nirB*	nitrite reductase flavoprotein
Rv0253	*nirD*	probable nitrite reductase small subunit

c. Electron transport

Rv0409	*ackA*	acetate kinase
Rv1623c	*appC*	cytochrome *bd-II* oxidase subunit I
Rv1622c	*cydB*	cytochrome *d* ubiquinol oxidase subunit II
Rv1620c	*cydC*	ABC transporter
Rv1621c	*cydD*	ABC transporter
Rv2007c	*fdxA*	ferredoxin
Rv3554	*fdxB*	ferredoxin
Rv1177	*fdxC*	ferredoxin 4Fe-4S
Rv3503c	*fdxD*	probable ferredoxin
Rv3029c	*fixA*	electron transfer flavoprotein subunit
Rv3028c	*fixB*	electron transfer flavoprotein subunit
Rv3106	*fprA*	adrenodoxin and NADPH ferredoxin reductase
Rv0886	*fprB*	ferredoxin, ferredoxin-NADP reductase
Rv3251c	*rubA*	rubredoxin A
Rv3250c	*rubB*	rubredoxin B

7. Miscellaneous oxidoreductases and oxygenases 171

8. ATP-proton motive force

Rv1308	*atpA*	ATP synthase chain
Rv1304	*atpB*	ATP synthase chain
Rv1311	*atpC*	ATP synthase ϵ chain
Rv1310	*atpD*	ATP synthase chain
Rv1305	*atpE*	ATP synthase c chain
Rv1306	*atpF*	ATP synthase b chain
Rv1309	*atpG*	ATP synthase chain
Rv1307	*atpH*	ATP synthase chain

C. Central intermediary metabolism

1. General

Rv2589	*gabT*	4-aminobutyrate aminotransferase
Rv3432c	*gadB*	glutamate decarboxylase
Rv1832	*gcvB*	glycine decarboxylase
Rv1826	*gcvH*	glycine cleavage system H protein
Rv2211c	*gcvT*	T protein of glycine cleavage system
Rv1213	*glgC*	glucose-1-phosphate adenylyltransferase
Rv3842c	*glpQ1*	glycerophosphoryl diester phosphodiesterase
Rv0317c	*glpQ2*	glycerophosphoryl diester phosphodiesterase
Rv3566c	*nhoA*	N-hydroxyarylamine *o*-acetyltransferase
Rv0155	*pntAA*	pyridine transhydrogenase subunit 1
Rv0156	pntAB	pyridine transhydrogenase subunit 2
Rv0157	*pntB*	pyridine transhydrogenase subunit
Rv1127c	*ppdK*	similar to pyruvate, phosphate dikinase

2. Gluconeogenesis

Rv0211	*pckA*	phosphoenolpyruvate carboxykinase
Rv0069c	*sdaA*	L-serine dehydratase 1

3. Sugar nucleotides

Rv1512	*epiA*	nucleotide sugar epimerase
Rv3784	*epiB*	probable UDP-galactose 4-epimerase
Rv1511	*gmdA*	GDP-mannose 4,6 dehydratase
Rv0334	*rmlA*	glucose-1-phosphate thymidyltransferase
Rv3264c	*rmlA2*	glucose-1-phosphate thymidyltransferase
Rv3464	*rmlB*	dTDP-glucose 4,6-dehydratase
Rv3634c	*rmlB2*	dTDP-glucose 4,6-dehydratase
Rv3468c	*rmlB3*	dTDP-glucose 4,6-dehydratase
Rv3465	*rmlC*	dTDP-4-dehydrorhamnose 3,5-epimerase
Rv3266c	*rmlD*	dTDP-4-dehydrorhamnose reductase
Rv0322	*udgA*	UDP-glucose dehydrogenase/GDP-mannose 6-dehydrogenase
Rv3265c	*wbbL*	dTDP-rhamnosyl transferase
Rv1525	*wbbl2*	dTDP-rhamnosyl transferase
Rv3400	-	probable -phosphoglucomutase

4. Amino sugars

Rv3436c	*glmS*	glucosamine-fructose-6-phosphate aminotransferase

5. Sulphur metabolism

Rv0711	*atsA*	arylsulfatase
Rv3299c	*atsB*	proable arylsulfatase
Rv0663	*atsD*	proable arylsulfatase
Rv3077	*atsF*	proable arylsulfatase
Rv0296c	*atsG*	proable arylsulfatase
Rv3796	*atsH*	proable arylsulfatase
Rv1285	*cysD*	ATP:sulphurylase subunit 2
Rv1286	*cysN*	ATP:sulphurylase subunit 1
Rv2131c	*cysQ*	homologue of *M.leprae cysQ*
Rv3248c	*sahH*	adenosylhomocysteinase
Rv3283	*sseA*	thiosulfate sulfurtransferase
Rv2291	*sseB*	thiosulfate sulfurtransferase
Rv3118	*sseC*	thiosulfate sulfurtransferase
Rv0814c	*sseC2*	thiosulfate sulfurtransferase
Rv3762c	-	probable alkyl sulfatase

D. Amino acid biosynthesis

1. Glutamate family

Rv1654	*argB*	acetylglutamate kinase
Rv1652	*argC*	N-acetyl- -glutamyl-phosphate reductase
Rv1655	*argD*	acetylornithine aminotransferase
Rv1656	*argF*	ornithine carbamoyltransferase
Rv1658	*argG*	arginosuccinate synthase
Rv1659	*argH*	arginosuccinate lyase
Rv1653	*argJ*	glutamate N-acetyltransferase
Rv2220	*glnA1*	glutamine synthase class I
Rv2222c	*glnA2*	glutamine synthase class II
Rv1878	*glnA3*	probable glutamine synthase
Rv2860c	*glnA4*	proable glutamine synthase
Rv2918c	*glnD*	uridylyltransferase
Rv2221c	*glnE*	glutamate-ammonia-ligase adenyltransferase
Rv3859c	*gltB*	ferredoxin-dependent glutamate synthase
Rv3858c	*gltD*	small subunit of NADH-dependent glutamate synthase
Rv3704c	*gshA*	possible -glutamylcysteine synthase
Rv2427c	*proA*	-glutamyl phosphate reductase
Rv2439c	*proB*	glutamate 5-kinase
Rv0500	*proC*	pyrroline-5-carboxylate reductase

2. Aspartate family

Rv3708c	*asd*	aspartate semialdehyde dehydrogenase
Rv3709c	*ask*	aspartokinase
Rv2201	*asnB*	asparagine synthase B
Rv3565	*aspB*	aspartate aminotransferase
Rv0337c	*aspC*	aspartate aminotransferase
Rv2753c	*dapA*	dihydrodipicolinate synthase
Rv2773c	*dapB*	dihydrodipicolinate reductase
Rv1202	*dapE*	succinyl-diaminopimelate desuccinylase
Rv2141c	*dapE2*	ArgE/DapE/Acy1/Cpg2/yscS family
Rv2726c	*dapF*	diaminopimelate epimerase
Rv1293	*lysA*	diaminopimelate decarboxylase
Rv3341	*metA*	homoserine *o*-acetyltransferase
Rv1079	*metB*	cystathionine -synthase
Rv3340	*metC*	cystathionine -lyase
Rv1133c	*metE*	5-methyltetrahydropteroyltriglutamate-homocysteine methyltransferase
Rv2124c	*metH*	5-methyltetrahydrofolate-homocysteine methyltransferase
Rv1392	*metK*	*S*-adenosylmethionine synthase
Rv0391	*metZ*	*o*-succinylhomoserine sulfhydrylase
Rv1294	*thrA*	homoserine dehydrogenase
Rv1296	*thrB*	homoserine kinase
Rv1295	*thrC*	homoserine synthase

3. Serine family

Rv0815c	*cysA2*	thiosulfate sulfurtransferase
Rv3117	*cysA3*	thiosulfate sulfurtransferase
Rv2335	*cysE*	serine acetyltransferase
Rv0511	*cysG*	uroporphyrin-III c-methyltransferase
Rv2847c	*cysG2*	multifunctional enzyme, siroheme synthase
Rv2334	*cysK*	cysteine synthase A
Rv1336	*cysM*	cysteine synthase B
Rv1077	*cysM2*	cystathionine -synthase
Rv0848	*cysM3*	putative cysteine synthase
Rv1093	*glyA*	serine hydroxymethyltransferase
Rv0070c	glyA2	serine hydroxymethyltransferase
Rv2996c	*serA*	D-3-phosphoglycerate dehydrogenase
Rv0505c	*serB*	probable phosphoserine phosphatase
Rv3042c	*serB2*	C-term similar to phosphoserine phosphatase
Rv0884c	*serC*	phosphoserine aminotransferase

4. Aromatic amino acid family

Rv3227	*aroA*	3-phosphoshikimate 1-carboxyvinyl transferase
Rv2538c	*aroB*	3-dehydroquinate synthase
Rv2537c	*aroD*	3-dehydroquinate dehydratase
Rv2552c	*aroE*	shikimate 5-dehydrogenase
Rv2540c	*aroF*	chorismate synthase
Rv2178c	*aroG*	DAHP synthase
Rv2539c	*aroK*	shikimate kinase I
Rv3838c	*pheA*	prephenate dehydratase
Rv1613	*trpA*	tryptophan synthase chain
Rv1612	*trpB*	tryptophan synthase chain
Rv1611	*trpC*	indole-3-glycerol phosphate synthase
Rv2192c	*trpD*	anthranilate phosphoribosyltransferase
Rv1609	*trpE*	anthranilate synthase component I
Rv2386c	*trpE2*	anthranilate synthase component I
Rv3754	*tyrA*	prephenate dehydrogenase

5. Histidine

Rv1603	*hisA*	phosphoribosylformimino-5-aminoimidazole carboxamide ribonucleotide isomerase
Rv1601	*hisB*	imidazole glycerol-phosphate dehydratase
Rv1600	*hisC*	histidinol-phosphate aminotransferase
Rv3772	*hisC2*	histidinol-phosphate aminotransferase
Rv1599	*hisD*	histidinol dehydrogenase

Nature © Macmillan Publishers Ltd 1998

Nature © Macmillan Publishers Ltd 1998

Rv1605	*hisF*	imidazole glycerol-phosphate synthase
Rv2121c	*hisG*	ATP phosphoribosyltransferase
Rv1602	*hisH*	amidotransferase
Rv2122c	*hisI*	phosphoribosyl-AMP cyclohydrolase
Rv1606	*hisI2*	probable phosphoribosyl-AMP 1,6 cyclohydrolase
Rv0114	-	similar to HisB

6. Pyruvate family

Rv3423c	*alr*	alanine racemase

7. Branched amino acid family

Rv1559	*ilvA*	threonine deaminase
Rv3003c	*ilvB*	acetolactate synthase I large subunit
Rv3470c	*ilvB2*	acetolactate synthase large subunit
Rv3001c	*ilvC*	ketol-acid reductoisomerase
Rv0189c	*ilvD*	dihydroxy-acid dehydratase
Rv2210c	*ilvE*	branched-chain-amino-acid transaminase
Rv1820	*ilvG*	acetolactate synthase II
Rv3002c	*ilvN*	acetolactate synthase I small subunit
Rv3509c	*ilvX*	probable acetohydroxyacid synthase I large subunit
Rv3710	*leuA*	-isopropyl malate synthase
Rv2995c	*leuB*	3-isopropylmalate dehydrogenase
Rv2988c	*leuC*	3-isopropylmalate dehydratase large subunit
Rv2987c	*leuD*	3-isopropylmalate dehydratase small subunit

E. Polyamine synthesis

Rv2601	*speE*	spermidine synthase

F. Purines, pyrimidines, nucleosides and nucleotides

1. Purine ribonucleotide biosynthesis

Rv1389	*gmk*	putative guanylate kinase
Rv3396c	*guaA*	GMP synthase
Rv1843c	*guaB1*	inosine-5'-monophosphate dehydrogenase
Rv3411c	*guaB2*	inosine-5'-monophosphate dehydrogenase
Rv3410c	*guaB3*	inosine-5'-monophosphate dehydrogenase
Rv1017c	*prsA*	ribose-phosphate pyrophosphokinase
Rv0357c	*purA*	adenylosuccinate synthase
Rv0777	*purB*	adenylosuccinate lyase
Rv0780	*purC*	phosphoribosylaminoimidazole-succinocarboxamide synthase
Rv0772	*purD*	phosphoribosylamine-glycine ligase
Rv3275c	*purE*	phosphoribosylaminoimidazole carboxylase
Rv0808	*purF*	amidophosphoribosyltransferase-
Rv0957	*purH*	phosphoribosylaminoimidazole-carboxamide formyltransferase
Rv3276c	*purK*	phosphoribosylaminoimidazole carboxylase ATPase subunit
Rv0803	*purL*	phosphoribosylformylglycin-amidine synthase II
Rv0809	*purM*	5'-phosphoribosyl-5-aminoimidazole synthase
Rv0956	*purN*	phosphoribosylglycinamide formyltransferase I
Rv0788	*purQ*	phosphoribosylformylglycin-amidine synthase I
Rv0389	*purT*	phosphoribosylglycinamide formyltransferase II
Rv2964	*purU*	formyltetrahydrofolate deformylase

2. Pyrimidine ribonucleotide biosynthesis

Rv1383	*carA*	carbamoyl-phosphate synthase subunit
Rv1384	*carB*	carbamoyl-phosphate synthase subunit
Rv1380	*pyrB*	aspartate carbamoyltransferase
Rv1381	*pyrC*	dihydroorotase
Rv2139	pyrD	dihydroorotate dehydrogenase
Rv1385	pyrF	orotidine 5'-phosphate decarboxylase
Rv1699	*pyrG*	CTP synthase
Rv2883c	*pyrH*	uridylate kinase
Rv0382c	*umpA*	probable uridine 5'-monophosphate synthase

3. 2'-deoxyribonucleotide metabolism

Rv0321	*dcd*	deoxycytidine triphosphate deaminase
Rv2697c	*dut*	deoxyuridine triphosphatase
Rv0233	*nrdB*	ribonucleoside-diphosphate reductase B2 (eukaryotic-like)
Rv3051c	*nrdE*	ribonucleoside diphosphate reductase chain
Rv1981c	*nrdF*	ribonucleotide reductase small subunit
Rv3048c	*nrdG*	ribonucleoside-diphosphate small subunit
Rv3053c	*nrdH*	glutaredoxin electron transport component of NrdEF system
Rv3052c	*nrdI*	NrdI/YgaO/YmaA family
Rv3247c	*tmk*	thymidylate kinase
Rv2764c	*thyA*	thymidylate synthase
Rv0570	*nrdZ*	ribonucleotide reductase, class II
Rv3752c	-	probable cytidine/deoxycytidylate deaminase

4. Salvage of nucleosides and nucleotides

Rv3313c	*add*	probable adenosine deaminase
Rv2584c	*apt*	adenine phosphoribosyltransferases
Rv3315c	*cdd*	probable cytidine deaminase
Rv3314c	*deoA*	thymidine phosphorylase
Rv0478	*deoC*	deoxyribose-phosphate aldolase
Rv3307	*deoD*	probable purine nucleoside phosphorylase
Rv3624c	*hpt*	probable hypoxanthine-guanine phosphoribosyltransferase
Rv3393	*iunH*	probable inosine-uridine preferring nucleoside hydrolase
Rv0535	*pnp*	phosphorylase from Pnp/MtaP family 2
Rv3309c	*upp*	uracil phophoribosyltransferase

5. Miscellaneous nucleoside/nucleotide reactions

Rv0733	*adk*	probable adenylate kinase
Rv2364c	*bex*	GTP-binding protein of Era/ThdF family
Rv1712	*cmk*	cytidylate kinase
Rv2344c	*dgt*	probable deoxyguanosine triphosphate hydrolase
Rv2404c	*lepA*	GTP-binding protein LepA
Rv2727c	*miaA*	tRNA (2)-isopentenylpyrophosphate transferase
Rv2445c	*ndkA*	nucleoside diphosphate kinase
Rv2440c	*obg*	Obg GTP-binding protein
Rv2583c	*relA*	(p)ppGpp synthase I

G. Biosynthesis of cofactors, prosthetic groups and carriers

1. Biotin

Rv1568	*bioA*	adenosylmethionine-8-amino-7-oxononanoate aminotransferase
Rv1589	*bioB*	biotin synthase
Rv1570	*bioD*	dethiobiotin synthase
Rv1569	*bioF*	8-amino-7-oxononanoate synthase
Rv0032	*bioF2*	C-terminal similar to *B. subtilis* BioF
Rv3279c	*birA*	biotin apo-protein ligase
Rv1442	*bisC*	biotin sulfoxide reductase
Rv0089	-	possible *bioC* biotin synthesis gene

2. Folic acid

Rv2763c	*dfrA*	dihydrofolate reductase
Rv2447c	*folC*	folylpolyglutamate synthase
Rv3356c	*folD*	methylenetetrahydrofolate dehydrogenase
Rv3609c	*folE*	GTP cyclohydrolase I
Rv3606c	*folK*	7,8-dihydro-6-hydroxymethylpterin pyrophosphokinase
Rv3608c	*folP*	dihydropteroate synthase
Rv1207	*folP2*	dihydropteroate synthase
Rv3607c	*folX*	may be involved in folate biosynthesis
Rv0013	*pabA*	*p*-aminobenzoate synthase glutamine amidotransferase
Rv1005c	*pabB*	*p*-aminobenzoate synthase
Rv0812	*pabC*	aminodeoxychorismate lyase

3. Lipoate

Rv2218	*lipA*	lipoate biosynthesis protein A
Rv2217	*lipB*	lipoate biosynthesis protein B

4. Molybdopterin

Rv3109	*moaA*	molybdenum cofactor biosynthesis, protein A
Rv0869c	*moaA2*	molybdenum cofactor biosynthesis, protein A
Rv0438c	*moaA3*	molybdenum cofactor biosynthesis, protein A
Rv3110	*moaB*	molybdenum cofactor biosynthesis, protein B
Rv0984	*moaB2*	molybdenum cofactor biosynthesis, protein B
Rv3111	*moaC*	molybdenum cofactor biosynthesis, protein C
Rv0864	*moaC2*	molybdenum cofactor biosynthesis, protein C
Rv3324c	*moaC3*	molybdenum cofactor biosynthesis, protein C
Rv3112	*moaD*	molybdopterin converting factor subunit 1
Rv0868c	*moaD2*	molybdopterin converting factor subunit 1
Rv3119	*moaE*	molybdopterin-converting factor subunit 2
Rv0866	*moaE2*	molybdopterin-converting factor subunit 2
Rv3322c	*moaE3*	molybdopterin-converting factor subunit 2
Rv0994	*moeA*	molybdopterin biosynthesis
Rv3116	*moeB*	molybdopterin biosynthesis
Rv2338c	*moeW*	molybdopterin biosynthesis
Rv1681	*moeX*	weak similarity to *E. coli* MoaA
Rv1355c	*moeY*	weak similarity to *E. coli* MoeB
Rv3206c	*moeZ*	probably involved in molybdopterin biosynthesis
Rv0865	*mog*	molybdopterin biosynthesis

5. Pantothenate

Rv1092c	*coaA*	pantothenate kinase
Rv2225	*panB*	3-methyl-2-oxobutanoate hydroxymethyltransferase
Rv3602c	*panC*	pantoate- -alanine ligase
Rv3601c	*panD*	aspartate 1-decarboxylase

6. Pyridoxine

Rv2607	*pdxH*	pyridoxamine 5'-phosphate oxidase

7. Pyridine nucleotide

Rv1594	*nadA*	quinolinate synthase
Rv1595	*nadB*	L-aspartate oxidase
Rv1596	*nadC*	nicotinate-nucleotide pyrophosphatase
Rv0423c	*thiC*	thiamine synthesis, pyrimidine moiety

8. Thiamine

Rv0422c	*thiD*	phosphomethylpyrimidine kinase
Rv0414c	*thiE*	thiamine synthesis, thiazole moiety
Rv0417	*thiG*	thiamine synthesis, thiazole moiety
Rv2977c	*thiL*	probable thiamine-monophosphate kinase

9. Riboflavin

Rv1940	*ribA*	GTP cyclohydrolase II
Rv1415	*ribA2*	probable GTP cyclohydrolase II
Rv1412	*ribC*	riboflavin synthase chain
Rv2671	*ribD*	probable riboflavin deaminase
Rv2786c	*ribF*	riboflavin kinase
Rv1409	*ribG*	riboflavin biosynthesis
Rv1416	*ribH*	riboflavin synthase chain
Rv3300c	-	probable deaminase, riboflavin synthesis

10. Thioredoxin, glutaredoxin and mycothiol

Rv0773c	*ggtA*	putative -glutamyl transpeptidase
Rv2394	*ggtB*	-glutamyltranspeptidase precursor
Rv2855	*gorA*	glutathione reductase homologue
Rv0816c	*thiX*	equivalent to *M. leprae* ThiX
Rv1470	*trxA*	thioredoxin
Rv1471	*trxB*	thioredoxin reductase
Rv3913	*trxB2*	thioredoxin reductase
Rv3914	*trxC*	thioredoxin

11. Menaquinone, PQQ, ubiquinone and other terpenoids

Rv2682c	*dxs*	1-deoxy-D-xylulose 5-phosphate synthase
Rv0562	*grcC1*	heptaprenyl diphosphate synthase II
Rv0989c	*grcC2*	heptaprenyl diphosphate synthase II
Rv3398c	*idsA*	geranylgeranyl pyrophosphate synthase
Rv2173	*idsA2*	geranylgeranyl pyrophosphate synthase
Rv3383c	*idsB*	transfergeranyl, similar geranyl pyrophosphate synthase
Rv0534c	*menA*	4-dihydroxy-2-naphthoate octaprenyltransferase
Rv0548c	*menB*	naphthoate synthase
Rv0553	*menC*	*o*-succinylbenzoate-CoA synthase
Rv0555	*menD*	2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate synthase
Rv0542c	*menE*	*o*-succinylbenzoic acid-CoA ligase
Rv3853	*menG*	*S*-adenosylmethionine: 2-demethylmenaquinone
Rv3397c	*phyA*	phytoene synthase
Rv0693	*pqqE*	coenzyme PQQ synthesis protein E
Rv0558	*ubiE*	ubiquinone/menaquinone biosynthesis methyltransferase

12. Heme and porphyrin

Rv0509	*hemA*	glutamyl-tRNA reductase
Rv0512	*hemB*	-aminolevulinic acid dehydratase
Rv0510	*hemC*	porphobilinogen deaminase
Rv2678c	*hemE*	uroporphyrinogen decarboxylase

Nature © Macmillan Publishers Ltd 1998

Nature © Macmillan Publishers Ltd 1998

Rv1300	*hemK*	protoporphyrinogen oxidase
Rv0524	*hemL*	glutamate-1-semialdehyde amino-transferase
Rv2388c	*hemN*	oxygen-independent coproporphyrinogen III oxidase
Rv2677c	*hemY'*	protoporphyrinogen oxidase
Rv1485	*hemZ*	ferrochelatase

13. Cobalamin

Rv2849c	*cobA*	cob(I)alamin adenosyltransferase
Rv2848c	*cobB*	cobyrinic acid a,c-diamide synthase
Rv2231c	*cobC*	aminotransferase
Rv2236c	*cobD*	cobinamide synthase
Rv2064	*cobG*	percorrin reductase
Rv2065	*cobH*	precorrin isomerase
Rv2066	*cobI*	CobI-CobJ fusion protein
Rv2070c	*cobK*	precorrin reductase
Rv2072c	*cobL*	probable methyltransferase
Rv2071c	*cobM*	precorrin-3 methylase
Rv2062c	*cobN*	cobalt insertion
Rv2208	*cobS*	cobalamin (5'-phosphate) synthase
Rv2207	*cobT*	nicotinate-nucleotide-dimethyl-benzimidazole transferase
Rv0254c	*cobU*	cobinamide kinase
Rv0255c	*cobQ*	cobyric acid synthase
Rv3713	*cobQ2*	possible cobyric acid synthase
Rv0306	-	similar to BluB cobalamin synthesis protein *R. capsulatus*

14. Iron utilization

Rv1876	*bfrA*	bacterioferritin
Rv3841	*bfrB*	bacterioferritin
Rv3215	*entC*	probable isochorismate synthase
Rv3214	*entD*	weak similarity to many phosphoglycerate mutases
Rv2895c	viuB	similar to proteins involved in vibriobactin uptake
Rv3525c	-	similar to ferripyochelin binding protein

H. Lipid biosynthesis

1. Synthesis of fatty and mycolic acids

Rv3285	*accA3*	acetyl/propionyl CoA carboxylase subunit
Rv0904c	*accD3*	acetyl/propionyl CoA carboxylase subunit
Rv3799c	*accD4*	acetyl/propionyl CoA carboxylase subunit
Rv3280	*accD5*	acetyl/propionyl CoA carboxylase subunit
Rv2247	*accD6*	acetyl/propionyl CoA carboxylase subunit
Rv2244	*acpM*	acyl carrier protein (meromycolate extension)
Rv2523c	*acpS*	CoA:apo-[ACP] pantethienephosphotransferase
Rv2243	*fabD*	malonyl CoA-[ACP] transacylase
Rv0649	*fabD2*	malonyl CoA-[ACP] transacylase
Rv1483	*fabG1*	3-oxoacyl-[ACP] reductase (aka MabA)
Rv1350	*fabG2*	3-oxoacyl-[ACP] Reductase
Rv2002	*fabG3*	3-oxoacyl-[ACP] reductase
Rv0242c	*fabG4*	3-oxoacyl-[ACP] reductase
Rv2766c	*fabG5*	3-oxoacyl-[ACP] reductase
Rv0533c	*fabH*	-ketoacyl-ACP synthase III
Rv2524c	*fas*	fatty acid synthase
Rv1484	*inhA*	enoyl-[ACP] reductase
Rv2245	*kasA*	-ketoacyl-ACP synthase (meromycolate extension)
Rv2246	*kasB*	-ketoacyl-ACP synthase (meromycolate extension)
Rv1618	*tesB1*	thioesterase II
Rv2605c	*tesB2*	thioesterase II
Rv0033	-	possible acyl carrier protein
Rv1344	-	possible acyl carrier protein
Rv1722	-	possible biotin carboxylase
Rv3221c	-	resembles biotin carboxyl carrier
Rv3472	-	possible acyl carrier protein

2. Modification of fatty and mycolic acids

Rv3391	*acrA1*	fatty acyl-CoA reductase
Rv3392c	*cmaA1*	cyclopropane mycolic acid synthase 1
Rv0503c	*cmaA2*	cyclopropane mycolic acid synthase 2
Rv0824c	*desA1*	acyl-[ACP] desaturase
Rv1094	*desA2*	acyl-[ACP] desaturase
Rv3229c	*desA3*	acyl-[ACP] desaturase
Rv0645c	*mmaA1*	methoxymycolic acid synthase 1
Rv0644c	*mmaA2*	methoxymycolic acid synthase 2
Rv0643c	*mmaA3*	methoxymycolic acid synthase 3
Rv0642c	*mmaA4*	methoxymycolic acid synthase 4
Rv0447c	*ufaA1*	unknown fatty acid methyltransferase
Rv3538	*ufaA2*	unknown fatty acid methyltransferase
Rv0469	*umaA1*	unknown mycolic acid methyltransferase
Rv0470c	*umaA2*	unknown mycolic acid methyltransferase

3. Acyltransferases, mycoloyltransferases and phospholipid synthesis

Rv2289	*cdh*	CDP-diacylglycerol phosphatidylhydrolase
Rv2881c	*cdsA*	phosphatidate cytidylyltransferase
Rv3804c	*fbpA*	antigen 85A, mycolyltransferase
Rv1886c	*fbpB*	antigen 85B, mycolyltransferase
Rv3803c	*fbpC1*	antigen 85C, mycolyltransferase
Rv0129c	*fbpC2*	antigen 85C', mycolyltransferase
Rv0564c	*gpdA1*	glycerol-3-phosphate dehydrogenase
Rv2982c	*gpdA2*	glycerol-3-phosphate dehydrogenase
Rv2612c	*pgsA*	CDP-diacylglycerol-glycerol-3-phosphate phosphatidyltransferase
Rv1822	*pgsA2*	CDP-diacylglycerol-glycerol-3-phosphate phosphatidyltransferase
Rv2746c	*pgsA3*	CDP-diacylglycerol-glycerol-3-phosphate phosphatidyltransferase
Rv1551	*plsB1*	glycerol-3-phosphate acyltransferase
Rv2482c	*plsB2*	glycerol-3-phosphate acyltransferase
Rv0437c	*psd*	putative phosphatidylserine decarboxylase
Rv0436c	*pssA*	CDP-diacylglycerol-serine *o*-phosphatidyltransferase
Rv0045c	-	possible dihydrolipoamide acetyltransferase
Rv0914c	-	lipid transfer protein
Rv1543	-	probable fatty-acyl CoA reductase
Rv1627c	-	lipid carrier protein
Rv1814	-	possible C-5 sterol desaturase
Rv1867	-	similar to acetyl CoA synthase/lipid carriers
Rv2261c	-	apolipoprotein N-acyltransferase-a
Rv2262c	-	apolipoprotein N-acyltransferase-b
Rv3523	-	lipid carrier protein
Rv3720	-	C-term similar to cyclopropane fatty acid synthases

I. Polyketide and non-ribosomal peptide synthesis

Rv2940c	*mas*	mycocerosic acid synthase
Rv2384	*mbtA*	mycobactin/exochelin synthesis (salicylate-AMP ligase)
Rv2383c	*mbtB*	mycobactin/exochelin synthesis (serine/threonine ligation)
Rv2382c	*mbtC*	mycobactin/exochelin synthesis
Rv2381c	*mbtD*	mycobactin/exochelin synthesis (polyketide synthase)
Rv2380c	*mbtE*	mycobactin/exochelin synthesis (lysine ligation)
Rv2379c	*mbtF*	mycobactin/exochelin synthesis (lysine ligation)
Rv2378c	*mbtG*	mycobactin/exochelin synthesis (lysine hydroxylase)
Rv2377c	*mbtH*	mycobactin/exochelin synthesis
Rv0101	*nrp*	unknown non-ribosomal peptide synthase
Rv1153c	*omt*	PKS *o*-methyltransferase
Rv3824c	*papA1*	PKS-associated protein, unknown function
Rv3820c	*papA2*	PKS-associated protein, unknown function
Rv1182	*papA3*	PKS-associated protein, unknown function
Rv1528c	*papA4*	PKS-associated protein, unknown function
Rv2939	*papA5*	PKS-associated protein, unknown function
Rv2946c	*pks1*	polyketide synthase
Rv1660	*pks10*	polyketide synthase (chalcone synthase-like)
Rv1665	*pks11*	polyketide synthase (chalcone synthase-like)
Rv2048c	*pks12*	polyketide synthase (erythronolide synthase-like)
Rv3800c	*pks13*	polyketide synthase
Rv1342c	*pks14*	polyketide synthase (chalcone synthase-like)
Rv2947c	*pks15*	polyketide synthase
Rv1013	*pks16*	polyketide synthase
Rv1663	*pks17*	polyketide synthase
Rv1372	*pks18*	polyketide synthase
Rv3825c	*pks2*	polyketide synthase
Rv1180	*pks3*	polyketide synthase
Rv1181	*pks4*	polyketide synthase
Rv1527c	*pks5*	polyketide synthase
Rv0405	*pks6*	polyketide synthase
Rv1661	*pks7*	polyketide synthase
Rv1662	*pks8*	polyketide synthase
Rv1664	*pks9*	polyketide synthase
Rv2931	*ppsA*	phenolpthiocerol synthesis (*pksB*)
Rv2932	*ppsB*	phenolpthiocerol synthesis (*pksC*)
Rv2933	*ppsC*	phenolpthiocerol synthesis (*pksD*)
Rv2934	*ppsD*	phenolpthiocerol synthesis (*pksE*)
Rv2935	*ppsE*	phenolpthiocerol synthesis (*pksF*)
Rv2928	*tesA*	thioesterase
Rv1544	-	probable ketoacyl reductase

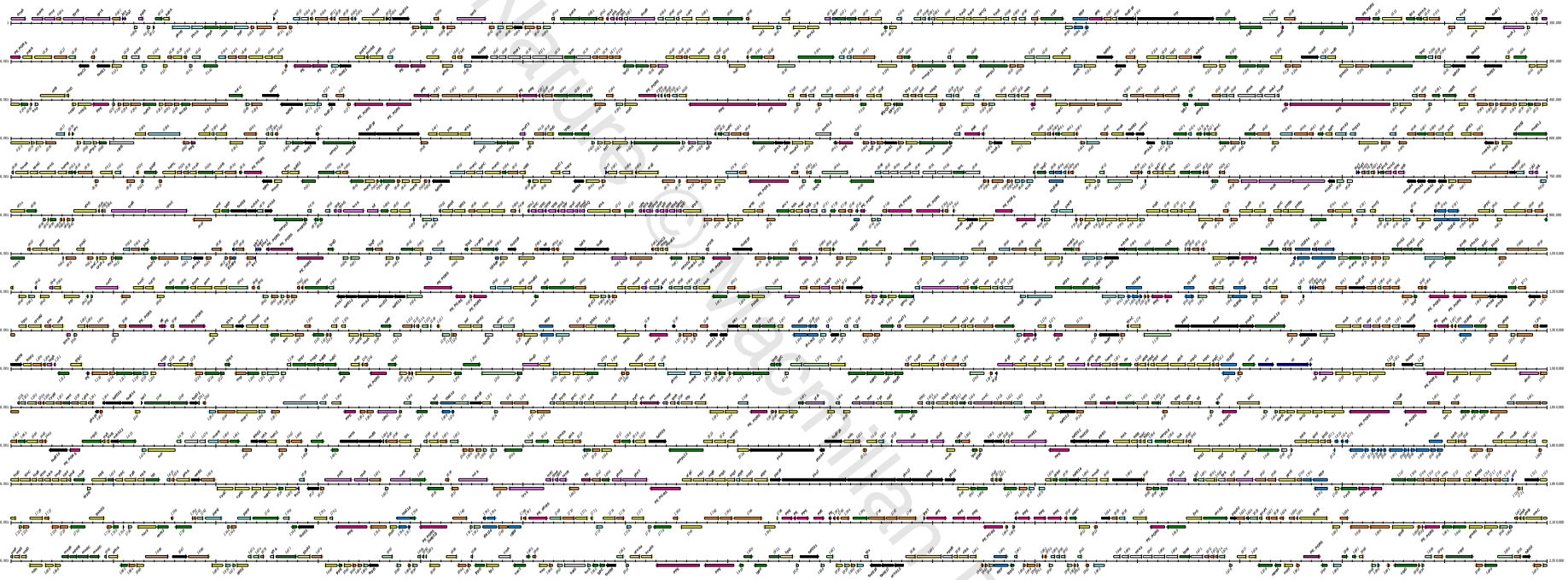
J. Broad regulatory functions

1. Repressors/activators

Rv1657	*argR*	arginine repressor
Rv1267c	*embR*	regulator of *embAB* genes (AfsR/DndI/RedD family)
Rv1909c	*furA*	ferric uptake regulatory protein
Rv2359	*furB*	ferric uptake regulatory protein
Rv2919c	*glnB*	nitrogen regulatory protein
Rv2711	*ideR*	iron dependent repressor, IdeR
Rv2720	*lexA*	LexA, SOS repressor protein
Rv1479	*moxR*	transcriptional regulator, MoxR homologue
Rv3692	*moxR2*	transcriptional regulator, MoxR homologue
Rv3164c	*moxR3*	transcriptional regulator, MoxR homologue
Rv0212c	*nadR*	similar to *E.coli* NadR
Rv0117	*oxyS*	transcriptional regulator (LysR family)
Rv1379	*pyrR*	regulatory protein pyrimidine biosynthesis
Rv2788	*sirR*	iron-dependent transcriptional repressor
Rv3082c	*virS*	putative virulence regulating protein (AraC/XylS family)
Rv3219	*whiB1*	WhiB transcriptional activator homologue
Rv3260c	*whiB2*	WhiB transcriptional activator homologue
Rv3416	*whiB3*	WhiB transcriptional activator homologue
Rv3681c	*whiB4*	WhiB transcriptional activator homologue
Rv0023	-	putative transcriptional regulator
Rv0043c	-	transcriptional regulator (GntR family)
Rv0067c	-	transcriptional regulator (TetR/AcrR family)
Rv0078	-	transcriptional regulator (TetR/AcrR family)
Rv0081	-	transcriptional regulator (ArsR family)
Rv0135c	-	putative transcriptional regulator
Rv0144	-	putative transcriptional regulator
Rv0158	-	transcriptional regulator (TetR/AcrR family)
Rv0165c	-	transcriptional regulator (GntR family)
Rv0195	-	transcriptional regulator (LuxR/UhpA family)
Rv0196	-	transcriptional regulator (TetR/AcrR family)
Rv0232	-	transcriptional regulator (TetR/AcrR family)
Rv0238	-	transcriptional regulator (TetR/AcrR family)
Rv0273c	-	putative transcriptional regulator
Rv0302	-	transcriptional regulator (TetR/AcrR family)
Rv0324	-	putative transcriptional regulator
Rv0328	-	transcriptional regulator (TetR/AcrR family)
Rv0348	-	putative transcriptional regulator
Rv0377	-	transcriptional regulator (LysR family)
Rv0386	-	transcriptional regulator (LuxR/UhpA family)
Rv0452	-	putative transcriptional regulator
Rv0465c	-	transcriptional regulator (PbsX/Xre family)
Rv0472c	-	transcriptional regulator (TetR/AcrR family)
Rv0474	-	transcriptional regulator (PbsX/Xre family)
Rv0485	-	transcriptional regulator (ROK family)
Rv0494	-	transcriptional regulator (GntR family)
Rv0552	-	putative transcriptional regulator
Rv0576	-	putative transcriptional regulator
Rv0586	-	transcriptional regulator (GntR family)
Rv0650	-	transcriptional regulator (ROK family)
Rv0653c	-	putative transcriptional regulator
Rv0681	-	transcriptional regulator (TetR/AcrR family)
Rv0691c	-	transcriptional regulator (TetR/AcrR family)
Rv0737	-	putative transcriptional regulator
Rv0744c	-	putative transcriptional regulator
Rv0792c	-	transcriptional regulator (GntR

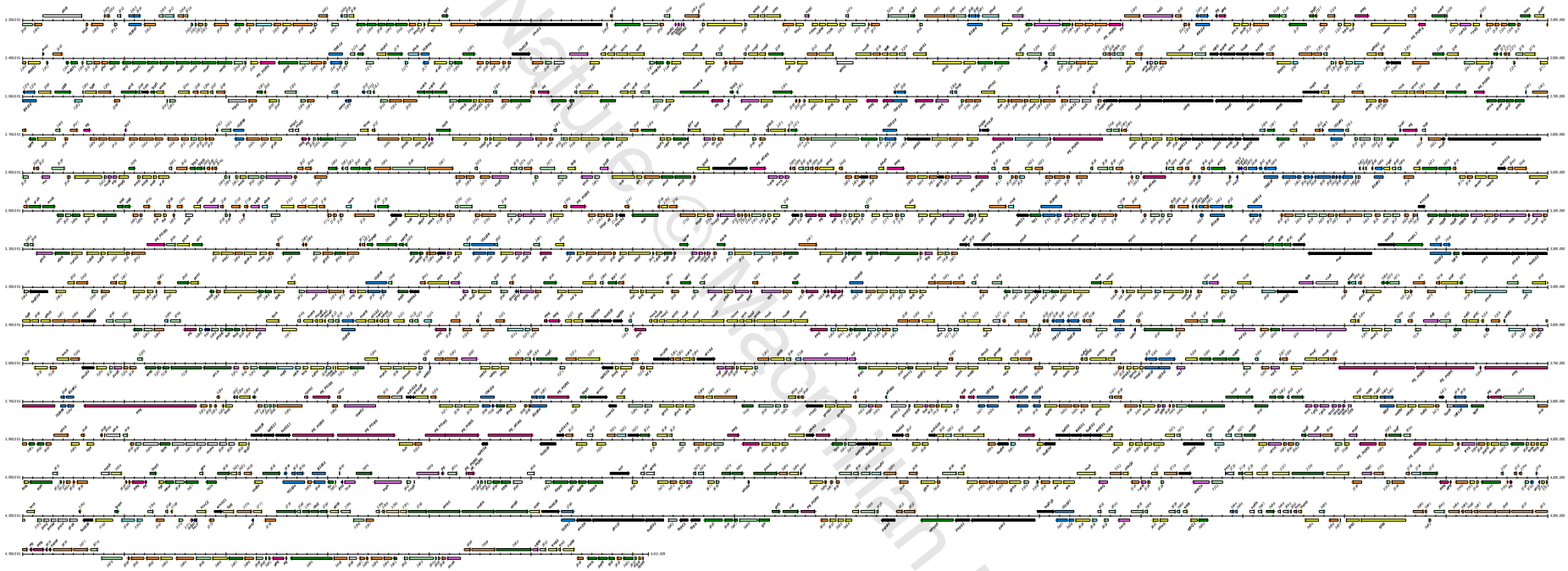
Nature © Macmillan Publishers Ltd 1998

Nature © Macmillan Publishers Ltd 1998



Nature © Macmillan Publishers Ltd 1998

Nature © Macmillan Publishers Ltd 1998



Nature © Macmillan Publishers Ltd 1998

Nature © Macmillan Publishers Ltd 1998

		family)
Rv0823c	-	transcriptional regulator (NifR3/Smm1 family)
Rv0827c	-	transcriptional regulator (ArsR family)
Rv0890c	-	transcriptional regulator (LuxR/UhpA family)
Rv0891c	-	putative transcriptional regulator
Rv0894	-	putative transcriptional regulator
Rv1019	-	transcriptional regulator (TetR/AcrR family)
Rv1049	-	transcriptional regulator (MarR family)
Rv1129c	-	transcriptional regulator (PbsX/Xre family)
Rv1151c	-	putative transcriptional regulator
Rv1152	-	transcriptional regulator (GntR family)
Rv1167c	-	putative transcriptional regulator
Rv1219c	-	putative transcriptional regulator
Rv1255c	-	transcriptional regulator (TetR/AcrR family)
Rv1332	-	putative transcriptional regulator
Rv1353c	-	transcriptional regulator (TetR/AcrR family)
Rv1358	-	transcriptional regulator (LuxR/UhpA family)
Rv1359	-	putative transcriptional regulator
Rv1395	-	transcriptional regulator (AraC/XylS family)
Rv1404	-	transcriptional regulator (MarR family)
Rv1423	-	putative transcriptional regulator
Rv1460	-	putative transcriptional regulator
Rv1474c	-	transcriptional regulator (TetR/AcrR family)
Rv1534	-	transcriptional regulator (TetR/AcrR family)
Rv1556	-	putative transcriptional regulator
Rv1674c	-	putative transcriptional regulator
Rv1675c	-	putative transcriptional regulator
Rv1719	-	transcriptional regulator (IclR family)
Rv1773c	-	transcriptional regulator (IclR family)
Rv1776c	-	putative transcriptional regulator
Rv1816	-	putative transcriptional regulator
Rv1846c	-	putative transcriptional regulator
Rv1931c	-	transcriptional regulator (AraC/XylS family)
Rv1956	-	putative transcriptional regulator
Rv1963c	-	putative transcriptional regulator
Rv1985c	-	transcriptional regulator (LysR family)
Rv1990c	-	putative transcriptional regulator
Rv1994c	-	transcriptional regulator (MerR family)
Rv2017	-	putative transcriptional regulator (PbsX/Xre family)
Rv2021c	-	putative transcriptional regulator
Rv2034	-	transcriptional regulator (ArsR family)
Rv2175c	-	putative transcriptional regulator
Rv2250c	-	putative transcriptional regulator
Rv2258c	-	putative transcriptional regulator
Rv2282c	-	transcriptional regulator (LysR family)
Rv2308	-	putative transcriptional regulator
Rv2324	-	transcriptional regulator (Lrp/AsnC family)
Rv2358	-	transcriptional regulator (ArsR family)
Rv2488c	-	transcriptional regulator (LuxR/UhpA family)
Rv2506	-	transcriptional regulator (TetR/AcrR family)
Rv2621c	-	putative transcriptional regulator
Rv2640c	-	transcriptional regulator (ArsR family)
Rv2642	-	transcriptional regulator (ArsR family)
Rv2669	-	putative transcriptional regulator
Rv2745c	-	putative transcriptional regulator
Rv2779c	-	transcriptional regulator (Lrp/AsnC family)
Rv2887	-	transcriptional regulator (MarR family)
Rv2912c	-	transcriptional regulator (TetR/AcrR family)
Rv2989	-	transcriptional regulator (IclR family)
Rv3050c	-	putative transcriptional regulator
Rv3055	-	putative transcriptional regulator
Rv3058c	-	putative transcriptional regulator
Rv3060c	-	transcriptional regulator (GntR family)
Rv3066	-	putative transcriptional regulator
Rv3095	-	putative transcriptional regulator
Rv3124	-	transcriptional regulator (AfsR/DndI/RedD family)
Rv3160c	-	putative transcriptional regulator
Rv3167c	-	putative transcriptional regulator
Rv3173c	-	transcriptional regulator (TetR/AcrR family)
Rv3183	-	putative transcriptional regulator
Rv3208	-	transcriptional regulator (TetR/AcrR family)
Rv3249c	-	transcriptional regulator (TetR/AcrR family)
Rv3291c	-	transcriptional regulator (Lrp/AsnC family)
Rv3295	-	transcriptional regulator (TetR/AcrR family)
Rv3334	-	transcriptional regulator (MerR family)
Rv3405c	-	putative transcriptional regulator
Rv3522	-	putative transcriptional regulator
Rv3557c	-	transcriptional regulator (TetR/AcrR family)
Rv3574	-	transcriptional regulator (TetR/AcrR family)
Rv3575c	-	transcriptional regulator (LacI family)
Rv3583c	-	putative transcriptional regulator
Rv3676	-	transcriptional regulator (Crp/Fnr family)
Rv3678c	-	transcriptional regulator (LysR family)
Rv3736	-	transcriptional regulator (AraC/XylS family)
Rv3744	-	transcriptional regulator (ArsR family)
Rv3830c	-	transcriptional regulator (TetR/AcrR family)
Rv3833	-	transcriptional regulator (AraC/XylS family)
Rv3840	-	putative transcriptional regulator
Rv3855	-	putative transcriptional regulator

2. Two component systems

Rv1028c	*kdpD*	sensor histidine kinase
Rv1027c	*kdpE*	two-component response regulator
Rv3246c	*mtrA*	two-component response regulator
Rv3245c	*mtrB*	sensor histidine kinase
Rv0844c	*narL*	two-component response regulator
Rv0757	*phoP*	two-component response regulator
Rv0758	*phoR*	sensor histidine kinase
Rv0491	*regX3*	two-component response regulator
Rv0490	*senX3*	sensor histidine kinase
Rv0602c	*tcrA*	two-component response regulator
Rv0260c	-	two-component response regulator
Rv0600c	-	sensor histidine kinase
Rv0601c	-	sensor histidine kinase
Rv0818	-	two-component response regulator
Rv0845	-	sensor histidine kinase
Rv0902c	-	sensor histidine kinase
Rv0903c	-	two-component response regulator
Rv0981	-	two-component response regulator
Rv0982	-	sensor histidine kinase
Rv1032c	-	sensor histidine kinase
Rv1033c	-	two-component response regulator
Rv1626	-	two-component response regulator
Rv2027c	-	sensor histidine kinase
Rv2884	-	two-component response regulator
Rv3132c	-	sensor histidine kinase
Rv3133c	-	two-component response regulator
Rv3143	-	putative sensory transduction protein
Rv3220c	-	sensor histidine kinase
Rv3764c	-	sensor histidine kinase
Rv3765c	-	two-component response regulator

3. Serine-threonine protein kinases and phosphoprotein phosphatases

Rv0015c	*pknA*	serine-threonine protein kinase
Rv0014c	*pknB*	serine-threonine protein kinase
Rv0931c	*pknD*	serine-threonine protein kinase
Rv1743	*pknE*	serine-threonine protein kinase
Rv1746	*pknF*	serine-threonine protein kinase
Rv0410c	*pknG*	serine-threonine protein kinase
Rv1266c	*pknH*	serine-threonine protein kinase
Rv2914c	*pknI*	serine-threonine protein kinase
Rv2088	*pknJ*	serine-threonine protein kinase
Rv3080c	*pknK*	serine-threonine protein kinase
Rv2176	*pknL*	serine-threonine protein kinase, truncated
Rv0018c	*ppp*	putative phosphoprotein phosphatase
Rv2234	*ptpA*	low molecular weight protein-tyrosine-phosphatase
Rv0153c	-	putative protein-tyrosine-phosphatase

II. Macromolecule metabolism

A. Synthesis and modification of macromolecules

1. Ribosomal protein synthesis and modification

Rv3420c	*rimI*	ribosomal protein S18 acetyl transferase
Rv0995	*rimJ*	acetylation of 30S S5 subunit
Rv0641	*rplA*	50S ribosomal protein L1
Rv0704	*rplB*	50S ribosomal protein L2
Rv0701	*rplC*	50S ribosomal protein L3
Rv0702	*rplD*	50S ribosomal protein L4
Rv0716	*rplE*	50S ribosomal protein L5
Rv0719	*rplF*	50S ribosomal protein L6
Rv0056	*rplI*	50S ribosomal protein L9
Rv0651	*rplJ*	50S ribosomal protein L10
Rv0640	*rplK*	50S ribosomal protein L11
Rv0652	*rplL*	50S ribosomal protein L7/L12
Rv3443c	*rplM*	50S ribosomal protein L13
Rv0714	*rplN*	50S ribosomal protein L14
Rv0723	*rplO*	50S ribosomal protein L15
Rv0708	*rplP*	50S ribosomal protein L16
Rv3456c	*rplQ*	50S ribosomal protein L17
Rv0720	*rplR*	50S ribosomal protein L18
Rv2904c	*rplS*	50S ribosomal protein L19
Rv1643	*rplT*	50S ribosomal protein L20
Rv2442c	*rplU*	50S ribosomal protein L21
Rv0706	*rplV*	50S ribosomal protein L22
Rv0703	*rplW*	50S ribosomal protein L23
Rv0715	*rplX*	50S ribosomal protein L24
Rv1015c	*rplY*	50S ribosomal protein L25
Rv2441c	*rpmA*	50S ribosomal protein L27
Rv0105c	*rpmB*	50S ribosomal protein L28
Rv2058c	*rpmB2*	50S ribosomal protein L28
Rv0709	*rpmC*	50S ribosomal protein L29
Rv0722	*rpmD*	50S ribosomal protein L30
Rv1298	*rpmE*	50S ribosomal protein L31
Rv2057c	*rpmG*	50S ribosomal protein L33
Rv3924c	*rpmH*	50S ribosomal protein L34
Rv1642	*rpmI*	50S ribosomal protein L35
Rv3461c	*rpmJ*	50S ribosomal protein L36
Rv1630	*rpsA*	30S ribosomal protein S1
Rv2890c	*rpsB*	30S ribosomal protein S2
Rv0707	*rpsC*	30S ribosomal protein S3
Rv3458c	*rpsD*	30S ribosomal protein S4
Rv0721	*rpsE*	30S ribosomal protein S5
Rv0053	*rpsF*	30S ribosomal protein S6
Rv0683	*rpsG*	30S ribosomal protein S7
Rv0718	*rpsH*	30S ribosomal protein S8
Rv3442c	*rpsI*	30S ribosomal protein S9
Rv0700	*rpsJ*	30S ribosomal protein S10
Rv3459c	*rpsK*	30S ribosomal protein S11
Rv0682	*rpsL*	30S ribosomal protein S12
Rv3460c	*rpsM*	30S ribosomal protein S13
Rv0717	*rpsN*	30S ribosomal protein S14
Rv2056c	*rpsN2*	30S ribosomal protein S14
Rv2785c	*rpsO*	30S ribosomal protein S15
Rv2909c	*rpsP*	30S ribosomal protein S16
Rv0710	*rpsQ*	30S ribosomal protein S17
Rv0055	*rpsR*	30S ribosomal protein S18
Rv2055c	*rpsR2*	30S ribosomal protein S18
Rv0705	*rpsS*	30S ribosomal protein S19
Rv2412	*rpsT*	30S ribosomal protein S20
Rv3241c	-	member of S30AE ribosomal protein family

2. Ribosome modification and maturation

Rv1010	*ksgA*	16S rRNA dimethyltransferase
Rv2838c	*rbfA*	ribosome-binding factor A
Rv2907c	*rimM*	16S rRNA processing protein

3. Aminoacyl tRNA synthases and their modification

Rv2555c	*alaS*	alanyl-tRNA synthase
Rv1292	argS	arginyl-tRNA synthase
Rv2572c	*aspS*	aspartyl-tRNA synthase
Rv3580c	*cysS*	cysteinyl-tRNA synthase
Rv2130c	*cysS2*	cysteinyl-tRNA synthase
Rv1406	*fmt*	methionyl-tRNA formyltransferase
Rv3011c	*gatA*	glu-tRNA-gln amidotransferase, subunit B
Rv3009c	*gatB*	glu-tRNA-gln amidotransferase, subunit A
Rv3012c	*gatC*	glu-tRNA-gln amidotransferase, subunit C
Rv2992c	*gltS*	glutamyl-tRNA synthase
Rv2357c	*glyS*	glycyl-tRNA synthase
Rv2580c	*hisS*	histidyl-tRNA synthase
Rv1536	*ileS*	isoleucyl-tRNA synthase
Rv0041	*leuS*	leucyl-tRNA synthase
Rv3598c	*lysS*	lysyl-tRNA synthase
Rv1640c	*lysX*	C-term lysyl-tRNA synthase
Rv1007c	*metS*	methionyl-tRNA synthase
Rv1649	*pheS*	phenylalanyl-tRNA synthase subunit

Nature © Macmillan Publishers Ltd 1998

Rv1650	*pheT*	phenylalanyl-tRNA synthase subunit
Rv2845c	*proS*	prolyl-tRNA synthase
Rv3834c	*serS*	seryl-tRNA synthase
Rv2614c	*thrS*	threonyl-tRNA synthase
Rv2906c	*trmD*	tRNA (guanine-N1)-methyltransferase
Rv3336c	*trpS*	tryptophanyl tRNA synthase
Rv1689	*tyrS*	tyrosyl-tRNA synthase
Rv2448c	*valS*	valyl-tRNA synthase

4. Nucleoproteins

Rv1407	*fmu*	similar to Fmu protein
Rv3852	*hns*	HU-histone protein
Rv2986c	*hupB*	DNA-binding protein II
Rv1388	*mIHF*	integration host factor

5. DNA replication, repair, recombination and restriction/modification

Rv1317c	*alkA*	DNA-3-methyladenine glycosidase II
Rv2836c	*dinF*	DNA-damage-inducible protein F
Rv1329c	*dinG*	probable ATP-dependent helicase
Rv3056	*dinP*	DNA-damage-inducible protein
Rv1537	*dinX*	probable DNA-damage-inducible protein
Rv0001	*dnaA*	chromosomal replication initiator protein
Rv0058	*dnaB*	DNA helicase (contains intein)
Rv1547	*dnaE1*	DNA polymerase III, subunit
Rv3370c	*dnaE2*	DNA polymerase III chain
Rv2343c	*dnaG*	DNA primase
Rv0002	*dnaN*	DNA polymerase III, subunit
Rv3711c	*dnaQ*	DNA polymerase III ε chain
Rv3721c	*dnaZX*	DNA polymerase III, (dnaZ) and (dnaX)
Rv2924c	*fpg*	formamidopyrimidine-DNA glycosylase
Rv0006	*gyrA*	DNA gyrase subunit A
Rv0005	*gyrB*	DNA gyrase subunit B
Rv2092c	*helY*	probable helicase, Ski2 subfamily
Rv2101	*helZ*	probable helicase, Snf2/Rad54 family
Rv2756c	*hsdM*	type I restriction/modification system DNA methylase
Rv2755c	*hsdS'*	type I restriction/modification system specificity determinant
Rv3296	*lhr*	ATP-dependent helicase
Rv3014c	*ligA*	DNA ligase
Rv3062	*ligB*	DNA ligase
Rv3731	*ligC*	probable DNA ligase
Rv1020	*mfd*	transcription-repair coupling factor
Rv2528c	*mrr*	restriction system protein
Rv2985	*mutT1*	MutT homologue
Rv1160	*mutT2*	MutT homologue
Rv0413	*mutT3*	MutT homologue
Rv3589	*mutY*	probable DNA glycosylase
Rv3297	*nei*	probable endonuclease VIII
Rv3674c	*nth*	probable endonuclease III
Rv1316c	*ogt*	methylated-DNA-protein-cysteine methyltransferase
Rv1629	*polA*	DNA polymerase I
Rv1402	*priA*	putative primosomal protein n' (replication factor Y)
Rv3585	*radA*	probable DNA repair RadA homologue
Rv2737c	*recA*	recombinase (contains intein)
Rv0630c	*recB*	exodeoxyribonuclease V
Rv0631c	*recC*	exodeoxyribonuclease V
Rv0629c	*recD*	exodeoxyribonuclease V
Rv0003	*recF*	DNA replication and SOS induction
Rv2973c	*recG*	ATP-dependent DNA helicase
Rv1696	*recN*	recombination and DNA repair
Rv3715c	*recR*	RecBC-Independent process of DNA repair
Rv2736c	*recX*	regulatory protein for RecA
Rv2593c	*ruvA*	Holliday junction binding protein, DNA helicase
Rv2592c	*ruvB*	Holliday junction binding protein
Rv2594c	*ruvC*	Holliday junction resolvase, endodeoxyribonuclease
Rv0054	*ssb*	single strand binding protein
Rv1210	*tagA*	DNA-3-methyladenine glycosidase I
Rv3646c	*topA*	DNA topoisomerase
Rv2976c	*ung*	uracil-DNA glycosylase
Rv1638	*uvrA*	excinuclease ABC subunit A
Rv1633	uvrB	excinuclease ABC subunit B
Rv1420	uvrC	excinuclease ABC subunit C
Rv0949	uvrD	DNA-dependent ATPase I and helicase II
Rv3198c	uvrD2	putative UvrD
Rv0427c	xthA	exodeoxyribonuclease III
Rv0071	-	group II intron maturase
Rv0861c	-	probable DNA helicase
Rv0944	-	possible formamidopyrimidine-DNA glycosylase
Rv1688	-	probable 3-methylpurine DNA glycosylase
Rv2090	-	partially similar to DNA polymerase I
Rv2191	-	similar to both PolC and UvrC proteins
Rv2464c	-	probable DNA glycosylase, endonuclease VIII
Rv3201c	-	probable ATP-dependent DNA helicase
Rv3202c	-	similar to UvrD proteins
Rv3263	-	probable DNA methylase
Rv3644c	-	similar in N-term to DNA polymerase III

6. Protein translation and modification

Rv0429c	*def*	polypeptide deformylase
Rv2534c	*efp*	elongation factor P
Rv2882c	*frr*	ribosome recycling factor
Rv0684	*fusA*	elongation factor G
Rv0120c	*fusA2*	elongation factor G
Rv1080c	*greA*	transcription elongation factor G
Rv3462c	*infA*	initiation factor IF-1
Rv2839c	*infB*	initiation factor IF-2
Rv1641	*infC*	initiation factor IF-3
Rv0009	*ppiA*	peptidyl-prolyl *cis-trans* isomerase
Rv2582	*ppiB*	peptidyl-prolyl *cis-trans* isomerase
Rv1299	*prfA*	peptide chain release factor 1
Rv3105c	*prfB*	peptide chain release factor 2
Rv2889c	*tsf*	elongation factor EF-Ts
Rv0685	tuf	elongation factor EF-Tu

7. RNA synthesis, RNA modification and DNA transcription

Rv1253	*deaD*	ATP-dependent DNA/RNA helicase
Rv2783c	*gpsI*	pppGpp synthase and polyribonucleotide phosphorylase
Rv2841c	*nusA*	transcription termination factor
Rv2533c	*nusB*	N-utilization substance protein B
Rv0639	*nusG*	transcription antitermination protein
Rv3907c	*pcnA*	polynucleotide polymerase
Rv3232c	*pvdS*	alternative sigma factor for siderophore production
Rv3211	*rhlE*	probable ATP-dependent RNA helicase
Rv1297	*rho*	transcription termination factor rho
Rv3457c	*rpoA*	subunit of RNA polymerase
Rv0667	*rpoB*	subunit of RNA polymerase
Rv0668	*rpoC*	' subunit of RNA polymerase
Rv1364c	*rsbU*	SigB regulation protein
Rv3287c	*rsbW*	anti-sigma B factor
Rv2703	*sigA*	RNA polymerase sigma factor (aka MysA, RpoV)
Rv2710	*sigB*	RNA polymerase sigma factor (aka MysB)
Rv2069	*sigC*	ECF subfamily sigma subunit
Rv3414c	*sigD*	ECF subfamily sigma subunit
Rv1221	*sigE*	ECF subfamily sigma subunit
Rv3286c	*sigF*	ECF subfamily sigma subunit
Rv0182c	*sigG*	sigma-70 factors ECF subfamily
Rv3223c	*sigH*	ECF subfamily sigma subunit
Rv1189	*sigI*	ECF family sigma factor
Rv3328c	*sigJ*	similar to SigI, ECF family
Rv0445c	*sigK*	ECF-type sigma factor
Rv0735	*sigL*	sigma-70 factors ECF subfamily
Rv3911	*sigM*	probable sigma factor, similar to SigE
Rv3366	*spoU*	probable rRNA methylase
Rv3455c	*truA*	probable pseudouridylate synthase
Rv2793c	*truB*	tRNA pseudouridine 55 synthase
Rv1644	*tsnR*	putative 23S rRNA methyltransferase
Rv3649	-	ATP-dependent DNA/RNA helicase

8. Polysaccharides (cytoplasmic)

Rv1326c	*glgB*	1,4- -glucan branching enzyme
Rv1328	*glgP*	probable glycogen phosphorylase
Rv1564c	*glgX*	probable glycogen debranching enzyme
Rv1563c	*glgY*	putative -amylase
Rv1562c	*glgZ*	maltooligosyltrehalose trehalohydrolase
Rv0126	-	probable glycosyl hydrolase
Rv1781c	-	probable 4- -glucanotransferase
Rv2471	-	probable maltase -glucosidase

B. Degradation of macromolecules

1. RNA

Rv1014c	*pth*	peptidyl-tRNA hydrolase
Rv2925c	*rnc*	RNAse III
Rv2444c	*rne*	similar at C-term to ribonuclease E
Rv2902c	*rnhB*	ribonuclease HII
Rv3923c	*rnpA*	ribonuclease P protein component
Rv1340	*rphA*	ribonuclease PH

2. DNA

Rv0670	*end*	endonuclease IV (apurinase)
Rv1108c	*xseA*	exonuclease VII large subunit
Rv1107c	*xseB*	exonuclease VII small subunit

3. Proteins, peptides and glycopeptides

Rv3305c	*amiA*	probable aminohydrolase
Rv3306c	*amiB*	probable aminohydrolase
Rv3596c	*clpC*	ATP-dependent Clp protease
Rv2461c	*clpP*	ATP-dependent Clp protease proteolytic subunit
Rv2460c	*clpP2*	ATP-dependent Clp protease proteolytic subunit
Rv2457c	*clpX*	ATP-dependent Clp protease ATP-binding subunit ClpX
Rv2667	*clpX'*	similar to ClpC from *M. leprae* but shorter
Rv3419c	*gcp*	glycoprotease
Rv2725c	*hflX*	GTP-binding protein
Rv1223	*htrA*	serine protease
Rv2861c	*map*	methionine aminopeptidase
Rv0734	*map'*	probable methionine aminopeptidase
Rv0319	*pcp*	pyrrolidone-carboxylate peptidase
Rv0125	*pepA*	probable serine protease
Rv2213	*pepB*	aminopeptidase A/I
Rv0800	*pepC*	aminopeptidase I
Rv2467	*pepD*	probable aminopeptidase
Rv2089c	*pepE*	cytoplasmic peptidase
Rv2535c	*pepQ*	cytoplasmic peptidase
Rv2782c	*pepR*	protease/peptidase, M16 family (insulinase)
Rv2109c	*prcA*	proteasome -type subunit 1
Rv2110c	*prcB*	proteasome -type subunit 2
Rv0782	*ptrBa*	protease II, subunit
Rv0781	*ptrBb*	protease II, subunit
Rv0724	*sppA*	protease IV, signal peptide peptidase
Rv0198c	-	probable zinc metalloprotease
Rv0457c	-	probable peptidase
Rv0840c	-	probable proline iminopeptidase
Rv0983	-	probable serine protease
Rv1977	-	probable zinc metallopeptidase
Rv3668c	-	probable alkaline serine protease
Rv3671c	-	probable serine protease
Rv3883c	-	probable secreted protease
Rv3886c	-	protease

4. Polysaccharides, lipopolysaccharides and phospholipids

Rv0062	*celA*	cellulase/endoglucanase
Rv3915	*cwlM*	hydrolase
Rv0315	-	probable -1,3-glucanase
Rv1090	-	probable inactivated cellulase/endoglucanase
Rv1327c	-	probable glycosyl hydrolase, -amylase family
Rv1333	-	probable hydrolase
Rv3463	-	probable neuraminidase
Rv3717	-	possible N-acetylmuramoyl-L-alanine amidase

5. Esterases and lipases

Rv0220	*lipC*	probable esterase
Rv1923	*lipD*	probable esterase
Rv3775	*lipE*	probable hydrolase
Rv3487c	*lipF*	probable esterase
Rv0646c	*lipG*	probable hydrolase
Rv1399c	*lipH*	probable lipase
Rv1400c	*lipI*	probable lipase
Rv1900c	*lipJ*	probable esterase
Rv2385	*lipK*	probable acetyl-hydrolase
Rv1497	*lipL*	esterase
Rv2284	*lipM*	probable esterase
Rv2970c	*lipN*	probable lipase/esterase
Rv1426c	*lipO*	probable esterase
Rv2463	*lipP*	probable esterase
Rv2485c	*lipQ*	probable carboxlyesterase
Rv3084	*lipR*	probable acetyl-hydrolase
Rv3176c	*lipS*	probable esterase/lipase
Rv2045c	*lipT*	probable carboxylesterase
Rv1076	*lipU*	probable esterase
Rv3203	*lipV*	probable lipase
Rv0217c	*lipW*	probable esterase
Rv2351c	*plcA*	phospholipase C precursor
Rv2350c	*plcB*	phospholipase C precursor
Rv2349c	*plcC*	phospholipase C precursor
Rv1755c	*plcD*	partial CDS for phospholipase C
Rv1104	-	probable esterase pseudogene
Rv1105	-	probable esterase pseudogene

6. Aromatic hydrocarbons

Rv3469c	*mhpE*	probable 4-hydroxy-2-oxovalerate aldolase
Rv0316	-	probable muconolactone isomerase
Rv0771	-	probable 4-carboxymuconolactone decarboxylase
Rv0939	-	probable dehydrase
Rv1723	-	6-aminohexanoate-dimer hydro-

Nature © Macmillan Publishers Ltd 1998

		lase
Rv2715	-	2-hydroxymuconic semialdehyde hydrolase
Rv3530c	-	probable *cis*-diol dehydrogenase
Rv3534c	-	4-hydroxy-2-oxovalerate aldolase
Rv3536c	-	aromatic hydrocarbon degradation

C. Cell envelope

1. Lipoproteins (*lppA-lpr0*) 65

2. Surface polysaccharides, lipopolysaccharides, proteins and antigens

Rv0806c	*cpsY*	probable UDP-glucose-4-epimerase
Rv3811	*csp*	secreted protein
Rv1677	*dsbF*	highly similar to C-term Mpt53
Rv3794	*embA*	involved in arabinogalactan synthesis
Rv3795	*embB*	involved in arabinogalactan synthesis
Rv3793	*embC*	involved in arabinogalactan synthesis
Rv3875	*esat6*	early secretory antigen target
Rv0112	*gca*	probable GDP-mannose dehydratase
Rv0113	*gmhA*	phosphoheptose isomerase
Rv2965c	*kdtB*	lipopolysaccharide core biosynthesis protein
Rv2878c	*mpt53*	secreted protein Mpt53
Rv1980c	*mpt64*	secreted immunogenic protein Mpb64/Mpt64
Rv2875	*mpt70*	major secreted immunogenic protein Mpt70 precursor
Rv2873	*mpt83*	surface lipoprotein Mpt83
Rv0899	*ompA*	member of OmpA family
Rv3810	*pirG*	cell surface protein precursor (Erp protein)
Rv3782	*rfbE*	similar to rhamnosyl transferase
Rv1302	*rfe*	undecaprenyl-phosphate -N-acetylglucosaminyltransferase
Rv2145c	*wag31*	antigen 84 (aka wag31)
Rv0431	-	tuberculin related peptide (AT103)
Rv0954	-	cell envelope antigen
Rv1514c	-	involved in polysaccharide synthesis
Rv1518	-	involved in exopolysaccharide synthesis
Rv1758	-	partial cutinase
Rv1910c	-	probable secreted protein
Rv1919c	-	weak similarity to pollen antigens
Rv1984c	-	probable secreted protein
Rv1987	-	probable secreted protein
Rv2223c	-	probable exported protease
Rv2224c	-	probable exported protease
Rv2301	-	probable cutinase
Rv2345	-	precursor of probable membrane protein
Rv2672	-	putative exported protease
Rv3019c	-	similar to Esat6
Rv3036c	-	probable secreted protein
Rv3449	-	probable precursor of serine protease
Rv3451	-	probable cutinase
Rv3452	-	probable cutinase precursor
Rv3724	-	probable cutinase precursor

3. Murein sacculus and peptidoglycan

Rv2911	*dacB*	penicillin binding protein
Rv2981c	*ddlA*	D-alanine-D-alanine ligase A
Rv3809c	*glf*	UDP-galactopyranose mutase
Rv1018c	*glmU*	UDP-N-acetylglucosamine pyrophosphorylase
Rv3382c	*lytB*	LytB protein homologue
Rv1110	*lytB'*	very similar to LytB
Rv1315	*murA*	UDP-N-acetylglucosamine-1-carboxyvinyltransferase
Rv0482	*murB*	UDP-N-acetylenolpyruvoylglucosamine reductase
Rv2152c	*murC*	UDP-N-acetyl-muramate-alanine ligase
Rv2155c	*murD*	UDP-N-acetylmuramoylalanine-D-glutamate ligase
Rv2158c	*murE*	*meso*-diaminopimelate-adding enzyme
Rv2157c	*murF*	D-alanine:D-alanine-adding enzyme
Rv2153c	*murG*	transferase in peptidoglycan synthesis
Rv1338	*murI*	glutamate racemase
Rv2156c	*murX*	phospho-N-acetylmuramoyl-petapeptide transferase
Rv3332	*nagA*	N-acetylglucosamine-6-P-deacetylase
Rv0016c	*pbpA*	penicillin-binding protein
Rv2163c	*pbpB*	penicillin-binding protein 2
Rv0050	*ponA*	penicillin-bonding protein
Rv3682	*ponA'*	class A penicillin binding protein
Rv0017c	*rodA*	FtsW/RodA/SpovE family
Rv0907	-	probable penicillin binding protein
Rv1367c	-	probable penicillin binding protein
Rv1730c	-	probable penicillin binding protein
Rv1922	-	probable penicillin binding protein
Rv2864c	-	probable penicillin binding protein
Rv3330	-	probable penicillin binding protein
Rv3627c	-	probable penicillin binding protein

4. Conserved membrane proteins

Rv0402c	*mmpL1*	conserved large membrane protein
Rv0507	*mmpL2*	conserved large membrane protein
Rv0206c	*mmpL3*	conserved large membrane protein
Rv0450c	*mmpL4*	conserved large membrane protein
Rv0676c	*mmpL5*	conserved large membrane protein
Rv1557	*mmpL6*	conserved large membrane protein
Rv2942	*mmpL7*	conserved large membrane protein
Rv3823c	*mmpL8*	conserved large membrane protein
Rv2339	*mmpL9*	conserved large membrane protein
Rv1183	*mmpL10*	conserved large membrane protein
Rv0202c	*mmpL11*	conserved large membrane protein
Rv1522c	*mmpL12*	conserved large membrane protein
Rv0403c	*mmpS1*	conserved small membrane protein
Rv0506	*mmpS2*	conserved small membrane protein
Rv2198c	*mmpS3*	conserved small membrane protein
Rv0451c	*mmpS4*	conserved small membrane protein
Rv0677c	*mmpS5*	conserved small membrane protein

5. Other membrane proteins 211

III. Cell processes

A. Transport/binding proteins

1. Amino acids

Rv2127	*ansP*	L-asparagine permease
Rv0346c	*aroP2*	probable aromatic amino acid permease
Rv0917	*betP*	glycine betaine transport
Rv1704c	*cycA*	transport of D-alanine, D-serine and glycine
Rv3666c	*dppA*	probable peptide transport system permease
Rv3665c	*dppB*	probable peptide transport system permease
Rv3664c	*dppC*	probable peptide transport system permease
Rv3663c	*dppD*	probable ABC-transporter
Rv0522	*gabP*	probable 4-amino butyrate transporter
Rv0411c	*glnH*	putative glutamine binding protein
Rv2564	*glnQ*	probable ATP-binding transport protein
Rv1280c	*oppA*	probable oligopeptide transport protein
Rv1283c	*oppB*	oligopeptide transport protein
Rv1282c	*oppC*	oligopeptide transport system permease
Rv1281c	*oppD*	probable peptide transport protein
Rv2320c	*rocE*	arginine/ornithine transporter
Rv3253c	-	probable cationic amino acid transport
Rv3454	-	possible proline permease

2. Cations

Rv2920c	*amt*	putative ammonium transporter
Rv1607	*chaA*	putative calcium/proton antiporter
Rv1239c	*corA*	probable magnesium and cobalt transport protein
Rv0092	*ctpA*	cation-transporting ATPase
Rv0103c	*ctpB*	cation transport ATPase
Rv3270	*ctpC*	cation transport ATPase
Rv1469	*ctpD*	probable cadmium-transporting ATPase
Rv0908	*ctpE*	probable cation transport ATPase
Rv1997	*ctpF*	probable cation transport ATPase
Rv1992c	*ctpG*	probable cation transport ATPase
Rv0425c	*ctpH*	C-terminal region putative cation-transporting ATPase
Rv0107c	*ctpI*	probable magnesium transport ATPase
Rv0969	*ctpV*	cation transport ATPase
Rv3044	*fecB*	putative FeIII-dicitrate transporter
Rv0265c	*fecB2*	iron transport protein FeIII dicitrate transporter
Rv1029	*kdpA*	potassium-transporting ATPase A chain
Rv1030	*kdpB*	potassium-transporting ATPase B chain
Rv1031	*kdpC*	potassium-transporting ATPase C chain
Rv3236c	*kefB*	probable glutathione-regulated potassium-efflux protein
Rv2877c	*merT*	possible mercury resistance transport system
Rv1811	*mgtC*	probable magnesium transport ATPase protein C
Rv0362	*mgtE*	putative magnesium ion transporter
Rv2856	*nicT*	probable nickel transport protein
Rv0924c	*nramp*	transmembrane protein belonging to Nramp family
Rv2691	*trkA*	probable potassium uptake protein
Rv2692	*trkB*	probable potassium uptake protein
Rv2287	*yjcE*	probable Na+/H+ exchanger
Rv2723	-	probable membrane protein, tellurium resistance
Rv3162c	-	probable membrane protein
Rv3237c	-	possible potassium channel protein
Rv3743c	-	probable cation-transporting ATPase

3. Carbohydrates, organic acids and alcohols

Rv2443	*dctA*	C4-dicarboxylate transport protein
Rv3476c	*kgtP*	sugar transport protein
Rv1902c	*nanT*	probable sialic acid transporter
Rv1236	*sugA*	membrane protein probably involved in sugar transport
Rv1237	*sugB*	sugar transport protein
Rv1238	*sugC*	ABC transporter component of sugar uptake system
Rv3331	*sugI*	probable sugar transport protein
Rv2835c	*ugpA*	*sn*-glycerol-3-phosphate permease
Rv2833c	*ugpB*	*sn*-glycerol-3-phosphate-binding periplasmic lipoprotein
Rv2832c	*ugpC*	*sn*-glycerol-3-phosphate transport ATP-binding protein
Rv2834c	*ugpE*	*sn*-glycerol-3-phosphate transport system protein
Rv2316	*uspA*	sugar transport protein
Rv2318	*uspC*	sugar transport protein
Rv2317	*uspE*	sugar transport protein
Rv1200	-	probable sugar transporter
Rv2038c	-	probable ABC sugar transporter
Rv2039c	-	probable sugar transporter
Rv2040c	-	probable sugar transporter
Rv2041c	-	probable sugar transporter

4. Anions

Rv2684	*arsA*	probable arsenical pump
Rv2685	*arsB*	probable arsenical pump
Rv3578	*arsB2*	probable arsenical pump
Rv2643	*arsC*	probable arsenical pump
Rv2397c	*cysA*	sulphate transport ATP-binding protein
Rv2399c	*cysT*	sulphate transport system permease protein
Rv2398c	*cysW*	sulphate transport system permease protein
Rv1857	*modA*	molybdate binding protein
Rv1858	*modB*	transport system permease, molybdate uptake
Rv1859	*modC*	molybdate uptake ABC-transporter
Rv1860	*modD*	precursor of Apa (45/47 kD secreted protein)
Rv2329c	*narK1*	probable nitrite extrusion protein
Rv1737c	*narK2*	nitrite extrusion protein
Rv0261c	*narK3*	nitrite extrusion protein1
Rv0267	*narU*	similar to nitrite extrusion protein 2
Rv0934	*phoS1*	PstS component of phosphate uptake
Rv0928	*phoS2*	PstS component of phosphate uptake
Rv0820	*phoT*	phosphate transport system ABC transporter
Rv3301c	*phoY1*	phosphate transport system regulator
Rv0821c	*phoY2*	phosphate transport system regulator
Rv0545c	*pitA*	low-affinity inorganic phosphate transporter
Rv2281	*pitB*	phosphate permease
Rv0930	*pstA1*	PstA component of phosphate uptake
Rv0936	*pstA2*	PstA component of phosphate uptake
Rv0933	*pstB*	ABC transport component of phosphate uptake
Rv0935	*pstC*	PstC component of phosphate uptake
Rv0929	*pstC2*	membrane-bound component of

Nature © Macmillan Publishers Ltd 1998

Nature © Macmillan Publishers Ltd 1998

		phosphate transport system
Rv0932c	*pstS*	PstS component of phosphate uptake
Rv2400c	*subI*	sulphate binding precursor
Rv0143c	-	probable chloride channel
Rv1707	-	probable sulphate permease
Rv1739c	-	possible sulphate transporter
Rv3679	-	possible anion transporter
Rv3680	-	probable anion transporter

5. Fatty acid transport

Rv2790c	*ltp1*	non-specific lipid transport protein
Rv3540c	*ltp2*	non-specific lipid transport protein

6. Efflux proteins

Rv2936	*drrA*	similar daunorubicin resistance ABC-transporter
Rv2937	*drrB*	similar daunorubicin resistance transmembrane protein
Rv2938	*drrC*	similar daunorubicin resistance transmembrane protein
Rv2846c	*efpA*	putative efflux protein
Rv3065	*emrE*	resistance to ethidium bromide
Rv0783c	-	multidrug resistance protein
Rv0849	-	possible quinolone efflux pump
Rv1145	-	probable drug transporter
Rv1146	-	probable drug transporter
Rv1250	-	probable drug efflux protein
Rv1258c	-	probable multidrug resistance pump
Rv1410c	-	probable drug efflux protein
Rv1634	-	probable drug efflux protein
Rv1819c	-	probable multidrug resistance pump
Rv2136c	-	putative bacitracin resistance protein
Rv2209	-	probable drug efflux protein
Rv2333c	-	probable tetracenomycin C resistance protein
Rv2994	-	probable fluoroquinolone efflux protein
Rv1877	-	probable drug efflux protein
Rv2459	-	probable drug efflux protein

B. Chaperones/Heat shock

Rv0384c	*clpB*	heat shock protein
Rv0352	*dnaJ*	acts with GrpE to stimulate DnaK ATPase
Rv2373c	*dnaJ2*	DnaJ homologue
Rv0350	*dnaK*	70 kD heat shock protein, chromosome replication
Rv3417c	*groEL1*	60 kD chaperonin 1
Rv0440	*groEL2*	60 kD chaperonin 2
Rv3418c	*groES*	10 kD chaperone
Rv0351	*grpE*	stimulates DnaK ATPase activity
Rv2374c	*hrcA*	heat-inducible transcription repressor
Rv0251c	*hsp*	possible heat shock protein
Rv0353	*hspR*	heat shock regulator
Rv2031c	*hspX*	14kD antigen, heat shock protein Hsp20 family
Rv2299c	*htpG*	heat shock protein Hsp90 family
Rv0563	*htpX*	probable (transmembrane) heat shock protein
Rv2701c	*suhB*	putative extragenic suppressor protein
Rv3269	-	probable heat shock protein

C. Cell division

Rv3641c	*fic*	possible cell division protein
Rv3102c	*ftsE*	membrane protein
Rv3610c	*ftsH*	inner membrane protein, chaperone
Rv2748c	*ftsK*	chromosome partitioning
Rv2151c	*ftsQ*	ingrowth of wall at septum
Rv2154c	*ftsW*	membrane protein (shape determination)
Rv3101c	*ftsX*	membrane protein
Rv2921c	*ftsY*	cell division protein FtsY
Rv2150c	*ftsZ*	circumferential ring, GTPase
Rv3919c	*gid*	glucose inhibited division protein B
Rv3625c	*mesJ*	probable cell cycle protein
Rv3917c	*parA*	chromosome partitioning; DNA - binding
Rv3918c	*parB*	possibly involved in chromosome partitioning
Rv2922c	*smc*	member of Smc1/Cut3/Cut14 family
Rv0012	-	possible cell division protein
Rv0435c	-	ATPase of AAA-family
Rv2115c	-	ATPase of AAA-family
Rv3213c	-	possible role in chromosome segregation
Rv1708	-	possible role in chromosome partitioning

D. Protein and peptide secretion

Rv2916c	*ffh*	signal recognition particle protein
Rv2903c	*lepB*	signal peptidase I
Rv1614	*lgt*	prolipoprotein diacylglyceryl transferase
Rv1539	*lspA*	lipoprotein signal peptidase
Rv0379	*sec*	probable transport protein SecE/Sec61- family
Rv3240c	*secA*	SecA, preprotein translocase subunit
Rv1821	*secA2*	SecA, preprotein translocase subunit
Rv2587c	*secD*	protein-export membrane protein
Rv0638	*secE*	SecE preprotein translocase
Rv2586c	*secF*	protein-export membrane protein
Rv1440	*secG*	protein-export membrane protein SecG
Rv0732	*secY*	SecY subunit of preprotein translocase
Rv2462c	*tig*	chaperone protein, similar to trigger factor
Rv2813	-	probable general secretion pathway protein

E. Adaptations and atypical conditions

Rv1901	*cinA*	competence damage protein
Rv3648c	*cspA*	cold shock protein, transcriptional regulator
Rv0871	*cspB*	probable cold shock protein
Rv3063	*cstA*	starvation-induced stress response protein
Rv3490	*otsA*	probable , -trehalose-phosphate synthase
Rv2006	*otsB*	trehalose-6-phosphate phosphatase
Rv3372	*otsB2*	trehalose-6-phosphate phosphatase
Rv3758c	*proV*	osmoprotection ABC transporter
Rv3757c	*proW*	transport system permease
Rv3759c	*proX*	similar to osmoprotection proteins
Rv3756c	*proZ*	transport system permease
Rv1026	-	probable pppGpp-5'phosphohydrolase

F. Detoxification

Rv2428	*ahpC*	alkyl hydroperoxide reductase
Rv2429	*ahpD*	member of AhpC/TSA family
Rv2238c	*ahpE*	member of AhpC/TSA family
Rv2521	*bcp*	bacterioferritin comigratory protein
Rv1608c	*bcpB*	probable bacterioferritin comigratory protein
Rv3473c	*bpoA*	probable non-heme bromoperoxidase
Rv1123c	*bpoB*	probable non-heme bromoperoxidase
Rv0554	*bpoC*	probable non-heme bromoperoxidase
Rv3617	*ephA*	probable epoxide hydrolase
Rv1938	*ephB*	probable epoxide hydrolase
Rv1124	*ephC*	probable epoxide hydrolase
Rv2214c	*ephD*	probable epoxide hydrolase
Rv3670	*ephE*	probable epoxide hydrolase
Rv0134	*ephF*	probable epoxide hydrolase
Rv3171c	*hpx*	probable non-heme haloperoxidase
Rv1908c	*katG*	catalase-peroxidase
Rv3846	*sodA*	superoxide dismutase
Rv0432	*sodC*	superoxide dismutase precursor - (Cu-Zn)
Rv1932	*tpx*	thiol peroxidase
Rv0634c	-	putative glyoxylase II
Rv2581c	-	putative glyoxylase II
Rv3177	-	probable non-heme haloperoxidase

IV. Other

A. Virulence

Rv0169	*mce1*	cell invasion protein
Rv0589	*mce2*	cell invasion protein
Rv1966	*mce3*	cell invasion protein
Rv3499c	*mce4*	cell invasion protein
Rv3100c	*smpB*	probable small protein b
Rv1694	*tlyA*	cytotoxin/hemolysin homologue
Rv0024	-	putative p60 homologue
Rv0167	-	part of *mce1* operon
Rv0168	-	part of *mce1* operon
Rv0170	-	part of *mce1* operon
Rv0171	-	part of *mce1* operon
Rv0172	-	part of *mce1* operon
Rv0174	-	part of *mce1* operon
Rv0587	-	part of *mce2* operon
Rv0588	-	part of *mce2* operon
Rv0590	-	part of *mce2* operon
Rv0591	-	part of *mce2* operon
Rv0592	-	part of *mce2* operon
Rv0594	-	part of *mce2* operon
Rv1085c	-	possible hemolysin
Rv1477	-	putative exported p60 protein homologue
Rv1478	-	putative exported p60 protein homologue
Rv1566c	-	putative exported p60 protein homologue
Rv1964	-	part of *mce3* operon
Rv1965	-	part of *mce3* operon
Rv1967	-	part of *mce3* operon
Rv1968	-	part of *mce3* operon
Rv1969	-	part of *mce3* operon
Rv1971	-	part of *mce3* operon
Rv2190c	-	putative p60 homologue
Rv3494c	-	part of *mce4* operon
Rv3496c	-	part of *mce4* operon
Rv3497c	-	part of *mce4* operon
Rv3498c	-	part of *mce4* operon
Rv3500c	-	part of *mce4* operon
Rv3501c	-	part of *mce4* operon
Rv3896c	-	putative p60 homologue
Rv3922c	-	possible hemolysin

B. IS elements, Repeated sequences, and Phage

1. IS elements

IS*6110*	16 copies
IS*1081*	6 copies
Others	37 copies

2. REP*13E12* family 7 copies

3. Phage-related functions

Rv2894c	*xerC*	integrase/recombinase
Rv1701	*xerD*	integrase/recombinase
Rv1054	-	integrase-a
Rv1055	-	integrase-b
Rv1573	-	phiRV1 phage related protein
Rv1574	-	phiRV1 phage related protein
Rv1575	-	phiRV1 phage related protein
Rv1576c	-	phiRV1 phage related protein
Rv1577c	-	phiRV1 possible prohead protease
Rv1578c	-	phiRV1 phage related protein
Rv1579c	-	phiRV1 phage related protein
Rv1580c	-	phiRV1 phage related protein
Rv1581c	-	phiRV1 phage related protein
Rv1582c	-	phiRV1 phage related protein
Rv1583c	-	phiRV1 phage related protein
Rv1584c	-	phiRV1 phage related protein
Rv1585c	-	phiRV1 phage related protein
Rv1586c	-	phiRV1 integrase
Rv2309c	-	integrase
Rv2310	-	excisionase
Rv2646	-	phiRV2 integrase
Rv2647	-	phiRV2 phage related protein
Rv2650c	-	phiRV2 phage related protein
Rv2651c	-	phiRV2 prohead protease
Rv2652c	-	phiRV2 phage related protein
Rv2653c	-	phiRV2 phage related protein
Rv2654c	-	phiRV2 phage related protein
Rv2655c	-	phiRV2 phage related protein
Rv2656c	-	phiRV2 phage related protein
Rv2657c	-	similar to gp36 of mycobacteriophage L5
Rv2658c	-	phiRV2 phage related protein
Rv2659c	-	phiRV2 integrase
Rv2830c	-	similar to phage P1 *phd* gene
Rv3750c	-	excisionase
Rv3751	-	putative integrase

C. PE and PPE families

1. PE family

PE subfamily	38 members
PE_PGRS subfamily	61 members

2. PPE family 68 members

D. Antibiotic production and resistance

Rv2068c	*blaC*	class A -lactamase
Rv3290c	*lat*	lysine-ε aminotransferase
Rv2043c	*pncA*	pyrazinamide resistance/sensitivity
Rv0133	-	possible puromycin N-acetyltransferase
Rv0262c	-	aminoglycoside 2'-N-acetyltransferase
Rv0802c	-	acetyltransferase
Rv1082	-	similar to *S. lincolnensis lmbE*
Rv1170	-	similar to *S. lincolnensis lmbE*
Rv1347c	-	possible aminoglycoside 6'-N-acetyltransferase
Rv2036	-	similar to lincomycin production genes
Rv2303c	-	similar to *S. griseus* macrotetrolide resistance protein
Rv3225c	-	probable aminoglycoside 3'-phosphotransferases
Rv3700c	-	probable acetyltransferase
Rv3817	-	probable aminoglycoside 3'-phosphotransferase

E. Bacteriocin-like proteins	3
F. Cytochrome P450 enzymes	22
G. Coenzyme F420-dependent enzymes	3
H. Miscellaneous transferases	61
I. Miscellaneous phosphatases, lyases, and hydrolases	18
J. Cyclases	6
K. Chelatases	2
V. Conserved hypotheticals	912
VI. Unknowns	606
TOTAL	3924

Nature © Macmillan Publishers Ltd 1998