**Supplementary file 1**

**Supplementary file 1a**

|  |  |  |
| --- | --- | --- |
| Number of *M. tuberculosis* isolates | Rifampicin MIC | Rifampicin 2 µg/mL as times of MIC  |
| 4 | 0.03 | 66.6 |
| 104 | 0.06 | 33.3 |
| 55 | 0.12 | 16.6 |
| 20 | 0.25 | 8.0 |
| 3 | 0.5 | 4.0 |

**Supplementary file 1b**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Patient number | trend\_group\_D5\_15 | trend\_group\_D5\_60 | *M. tb* isolate collection (in months) | Compari-sion between two isolates | SNP differe-nce | isolate 1 | isolate 2 | amino\_acid change | Locus\_gene | product | gene | locus\_tag | Repetitive-e\_region |  |
| 1 | Increase | Increase | 0M, 1M, 8M | 0M, 1M | 0 | NA | ad\_ratio:0.9 | E52G | Rv1793 (esxN) | ESAT-6 like protein EsxN | esxN | Rv1793 | FALSE |  |
| 1 | Increase | Increase | 0M, 1M, 8M | 0M, 1M | 0 | NA | ad\_ratio:0.9 | N38S | Rv2543 (lppA) | lipoprotein LppA | lppA | Rv2543 | FALSE |  |
| 1 | Increase | Increase | 0M, 1M, 8M | 0M, 1M | 0 | NA | ad\_ratio:0.9 | R278H | Rv3138 (pflA) | pyruvate formate lyase activating protein PflA | pflA | Rv3138 | FALSE |  |
| 1 | Increase | Increase | 0M, 1M, 8M | 0M, 1M | 0 | ad\_ratio:0.9 | NA | R389W | Rv1319c (NA) | adenylate cyclase | NA | Rv1319c | FALSE |  |
| 2 | Increase | Decrease | 0M, 1M, 12M | 0M, 1M | 0 | NA | ad\_ratio:0.9 | H37Q | Rv2543 (lppA) | lipoprotein LppA | lppA | Rv2543 | FALSE |  |
| 2 | Increase | Decrease | 0M, 1M, 12M | 0M, 1M | 0 | NA | ad\_ratio:0.9 | N38S | Rv2543 (lppA) | lipoprotein LppA | lppA | Rv2543 | FALSE |  |
| 3 | Increase | Unchange | 0M, 1M | 0M, 1M | 3 | NA | ad\_ratio:0.9 | G407V | Rv1266c (pknH) | serine/threonine-protein kinase PknH | pknH | Rv1266c | FALSE |  |
| 3 | Increase | Unchange | 0M, 1M | 0M, 1M | 3 | NA | ad\_ratio:0.9 | L404F | Rv1266c (pknH) | serine/threonine-protein kinase PknH | pknH | Rv1266c | FALSE |  |
| 3 | Increase | Unchange | 0M, 1M | 0M, 1M | 3 | NA | ad\_ratio:0.9 | G174R | Rv2351c (plcA) | membrane-associated phospholipase A | plcA | Rv2351c | FALSE |  |
| 3 | Increase | Unchange | 0M, 1M | 0M, 1M | 3 | NA | ad\_ratio:0.9 | I171V | Rv2351c (plcA) | membrane-associated phospholipase A | plcA | Rv2351c | FALSE |  |
| 3 | Increase | Unchange | 0M, 1M | 0M, 1M | 3 | NA | ad\_ratio:0.9 | T168A | Rv2351c (plcA) | membrane-associated phospholipase A | plcA | Rv2351c | FALSE |  |
| 3 | Increase | Unchange | 0M, 1M | 0M, 1M | 3 | NA | PASS | P5L | Rv2802c (NA) | arginine/hypothetical protein | NA | Rv2802c | FALSE |  |
| 3 | Increase | Unchange | 0M, 1M | 0M, 1M | 3 | NA | ad\_ratio:0.9 | A38G | Rv3901c (NA) | membrane protein | NA | Rv3901c | FALSE |  |
| 3 | Increase | Unchange | 0M, 1M | 0M, 1M | 3 | NA | ad\_ratio:0.9 | T16I | Rv3901c (NA) | membrane protein | NA | Rv3901c | FALSE |  |
| 3 | Increase | Unchange | 0M, 1M | 0M, 1M | 3 | ad\_ratio:0.9 | NA | R6G | Rv1758 (cut1) | cutinase | cut1 | Rv1758 | FALSE |  |
| 3 | Increase | Unchange | 0M, 1M | 0M, 1M | 3 | PASS | NA | I463S | Rv2488c (NA) | LuxR family transcriptional regulator | NA | Rv2488c | FALSE |  |
| 3 | Increase | Unchange | 0M, 1M | 0M, 1M | 3 | PASS | NA | S128W | Rv2828c (NA) | hypothetical protein | NA | Rv2828c | FALSE |  |
| 4 | Increase | Increase | 0M, 1M, 2M, 12M, | 0M, 12M | 0 | NA | ad\_ratio:0.9 | T178A | Rv0792c (NA) | transcriptional regulator | NA | Rv0792c | FALSE |  |
| 4 | Increase | Increase | 0M, 1M, 2M, 12M, | 0M, 12M | 0 | NA | ad\_ratio:0.9 | D48E | Rv1907c (NA) | hypothetical protein | NA | Rv1907c | FALSE |  |
| 4 | Increase | Increase | 0M, 1M, 2M, 12M, | 0M, 12M | 0 | NA | ad\_ratio:0.9 | V96A | Rv3424c (NA) | hypothetical protein | NA | Rv3424c | FALSE |  |
| 4 | Increase | Increase | 0M, 1M, 2M, 12M, | 0M, 12M | 0 | ad\_ratio:0.9 | NA | R389W | Rv1319c (NA) | adenylate cyclase | NA | Rv1319c | FALSE |  |
| 4 | Increase | Increase | 0M, 1M, 2M, 12M, | 0M, 12M | 0 | ad\_ratio:0.9 | NA | N378D | Rv3680 (NA) | anion transporter ATPase | NA | Rv3680 | FALSE |  |
| 5 | Increase | Decrease | 0M, 24M | 0M, 24M | 3 | NA | PASS | L69F | Rv2329c (narK1) | nitrate/nitrite transporter | narK1 | Rv2329c | FALSE |  |
| 5 | Increase | Decrease | 0M, 24M | 0M, 24M | 3 | ad\_ratio:0.9 | NA | R389W | Rv1319c (NA) | adenylate cyclase | NA | Rv1319c | FALSE |  |
| 7 | Increase | Decrease | 0M, 1M, 18M | 0M, 1M | 0 | NA | ad\_ratio:0.9 | V96A | Rv3424c (NA) | hypothetical protein | NA | Rv3424c | FALSE |  |
| 8 | Increase | Increase | 0M, 2M | 0M, 2M | 0 | NA | ad\_ratio:0.9 | D48E | Rv1907c (NA) | hypothetical protein | NA | Rv1907c | FALSE |  |
| 9 | Increase | Increase | 0M, 1M, 12M | 0M, 12M | 3 | NA | PASS | R566H | Rv0973c (accA2) | acetyl/propionyl-CoA carboxylase subuit alpha | accA2 | Rv0973c | FALSE |  |
| 9 | Increase | Increase | 0M, 1M, 12M | 0M, 12M | 3 | NA | PASS | W205\* | Rv1270c (lprA) | lipoprotein LprA | lprA | Rv1270c | FALSE |  |
| 9 | Increase | Increase | 0M, 1M, 12M | 0M, 12M | 3 | NA | ad\_ratio:0.9 | D439E | Rv1319c (NA) | adenylate cyclase | NA | Rv1319c | FALSE |  |
| 9 | Increase | Increase | 0M, 1M, 12M | 0M, 12M | 3 | NA | PASS | D191G | Rv3483c (NA) | hypothetical protein | NA | Rv3483c | FALSE |  |
| 12 | Unchange | Increase | 0M, 8M | 0M, 8M | 1 | ad\_ratio:0.9 | NA | R389W | Rv1319c (NA) | adenylate cyclase | NA | Rv1319c | FALSE |  |
| 12 | Unchange | Increase | 0M, 8M | 0M, 8M | 1 | ad\_ratio:0.9 | NA | N378D | Rv3680 (NA) | anion transporter ATPase | NA | Rv3680 | FALSE |  |
| 13 | Unchange | Unchange | 0M, 12M | 0M, 12M | 3 | NA | PASS | Q126K | Rv2083 (NA) | hypothetical protein | NA | Rv2083 | FALSE |  |
| 13 | Unchange | Unchange | 0M, 12M | 0M, 12M | 3 | ad\_ratio:0.9 | NA | R389W | Rv1319c (NA) | adenylate cyclase | NA | Rv1319c | FALSE |  |
| 13 | Unchange | Unchange | 0M, 12M | 0M, 12M | 3 | ad\_ratio:0.9 | NA | G323S | Rv2318 (uspC) | sugar ABC transporter substrate-binding lipoprotein UspC | uspC | Rv2318 | FALSE |  |
| 13 | Unchange | Unchange | 0M, 12M | 0M, 12M | 3 | PASS | NA | G191R | Rv2836c (dinF) | DNA-damage-inducible protein DinF | dinF | Rv2836c | FALSE |  |
| 13 | Unchange | Unchange | 0M, 12M | 0M, 12M | 3 | PASS | NA | V164M | Rv2893 (NA) | oxidoreductase | NA | Rv2893 | FALSE |  |
| 14 | Decrease | Decrease | 0M, 18M | 0M, 18M | 3 | NA | ad\_ratio:0.9 | G292S | Rv1997 (ctpF) | cation transporter ATPase F | ctpF | Rv1997 | FALSE |  |
| 14 | Decrease | Decrease | 0M, 18M | 0M, 18M | 3 | NA | PASS | H347Y | Rv2394 (ggtB) | gamma-glutamyltranspeptidase precursor GgtB | ggtB | Rv2394 | FALSE |  |
| 14 | Decrease | Decrease | 0M, 18M | 0M, 18M | 3 | NA | PASS | P188S | Rv2728c (NA) | hypothetical protein | NA | Rv2728c | FALSE |  |
| 14 | Decrease | Decrease | 0M, 18M | 0M, 18M | 3 | PASS | NA | W12R | Rv1899c (lppD) | lipoprotein LppD | lppD | Rv1899c | FALSE |  |
| 16 | Decrease | Increase | 0M, 5M | 0M, 5M | 2 | NA | PASS | M382I | Rv1704c (cycA) | D-serine/alanine/glycine transporter protein CycA | cycA | Rv1704c | FALSE |  |
| 16 | Decrease | Increase | 0M, 5M | 0M, 5M | 2 | NA | ad\_ratio:0.9 | V73A | Rv1883c (NA) | hypothetical protein | NA | Rv1883c | FALSE |  |
| 16 | Decrease | Increase | 0M, 5M | 0M, 5M | 2 | ad\_ratio:0.9 | NA | I171V | Rv2351c (plcA) | membrane-associated phospholipase A | plcA | Rv2351c | FALSE |  |
| 16 | Decrease | Increase | 0M, 5M | 0M, 5M | 2 | ad\_ratio:0.9 | NA | T168A | Rv2351c (plcA) | membrane-associated phospholipase A | plcA | Rv2351c | FALSE |  |
| 16 | Decrease | Increase | 0M, 5M | 0M, 5M | 2 | ad\_ratio:0.9 | NA | A139T | Rv2543 (lppA) | lipoprotein LppA | lppA | Rv2543 | FALSE |  |
| 17 | Decrease | Increase | 1M, 8M | 1M, 8M | 11 | NA | PASS | Y1638H | Rv0101 (nrp) | peptide synthetase Nrp | nrp | Rv0101 | FALSE |  |
| 17 | Decrease | Increase | 1M, 8M | 1M, 8M | 11 | NA | PASS | R384W | Rv1696 (recN) | DNA repair protein RecN | recN | Rv1696 | FALSE |  |
| 17 | Decrease | Increase | 1M, 8M | 1M, 8M | 11 | NA | PASS | Q10\* | Rv2043c (pncA) | pyrazinamidase/nicotinamidase PncA | pncA | Rv2043c | FALSE |  |
| 17 | Decrease | Increase | 1M, 8M | 1M, 8M | 11 | NA | PASS | K342E | Rv2400c (subI) | sulfate ABC transporter substrate-binding lipoprotein SubI | subI | Rv2400c | FALSE |  |
| 17 | Decrease | Increase | 1M, 8M | 1M, 8M | 11 | NA | PASS | P43R | Rv2544 (lppB) | lipoprotein LppB | lppB | Rv2544 | FALSE |  |
| 17 | Decrease | Increase | 1M, 8M | 1M, 8M | 11 | NA | PASS | H44R | Rv2544 (lppB) | lipoprotein LppB | lppB | Rv2544 | FALSE |  |
| 17 | Decrease | Increase | 1M, 8M | 1M, 8M | 11 | NA | ad\_ratio:0.9 | L33F | Rv2545 (vapB18) | antitoxin VapB18 | vapB18 | Rv2545 | FALSE |  |
| 17 | Decrease | Increase | 1M, 8M | 1M, 8M | 11 | NA | PASS | P335L | Rv2689c (NA) | hypothetical protein | NA | Rv2689c | FALSE |  |
| 17 | Decrease | Increase | 1M, 8M | 1M, 8M | 11 | ad\_ratio:0.9 | NA | V73A | Rv1883c (NA) | hypothetical protein | NA | Rv1883c | FALSE |  |
| 17 | Decrease | Increase | 1M, 8M | 1M, 8M | 11 | PASS | NA | L80P | Rv2398c (cysW) | sulfate ABC transporter permease CysW | cysW | Rv2398c | FALSE |  |
| 18 | Decrease | Increase | 0M, 12M, 18M | 0M, 18M | 3 | NA | PASS | F209L | Rv3758c (proV) | glycine betaine/carnitine/choline/L-proline ABC transporter ATP-binding protein ProV | proV | Rv3758c | FALSE |  |

NA - Wild-type

ad\_ratio:0.9 - Emerging Non-synonymous SNP in reads below 90% threshold.

Pass - Emerging Non-synonymous SNP in reads above 90% threshold.

Note: SNPs difference include both synonymous and nonsynonymous variants (only Pass).

**Supplementary file 1c**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Gene name | Mutation | Gene function  | Associated change rifampicin tolerance – D5-15 | Associated change rifampicin tolerance – D5-60 | Reported function related to survival or antibiotic response | Reference |
| Rv0101 | Y1638H | Probable peptide synthetase nrp | Decrease | Increase | * Down regulated upon rifampicin exposure of MDR-H37Rv
* Prevented INH-mediated killing *M. tuberculosis* in Mice
 | Knegt et. al., 2013Dhar and McKinney 2010 |
| Rv0792c | T178A | Probable transcription regulatory protein (gntr family) | Increase | Increase | Gene upregulated in *M. tuberculosis* persisters. | Keren et. al., 2011 |
| Rv0973c | R566H | Lipid metabolism | Increase | Increase | Gene downregulated upon HigB toxin expression in *M. tuberculosis* | Schuessler et. al., 2013 |
| Rv1266c | G407V | *pknH*, Serine/threonine protein kinase | Increase | No change | Interaction partner of FtsB in *M. tuberculosis,* regulation of cell division during persistence. | Wang et. al., 2019 |
| L404F | Increase | No change |
| Rv1270c | W205\* | *lprA*, Cell wall and cell processes | Increase | Increase | Gene upregulated upon *sigF* induction | Williams et. al., 2007 |
| Rv1319c | D439E | Putative adenylate cyclase, regulation of cellular metabolism | Increase | Increase | Gene displaying high within-host genetic diversity. | Nimmo et. al., 2020 |
| R389W | Increase (n = 3), No change (n = 2), Decrease (n = 1). | Increase (n = 3), no change (n = 1), decrease (n = 1). |
| Rv1696 | R384W | *RccN*, works in DNA repair | Decrease | Increase | DNA repair mechanism in *M. tuberculosis* | Mittal et. al., 2020 |
| Rv1704c | M382I | Alanine transporter CycA | Decrease | Increase | Gene involved in D-cycloserine resistance | Vilcheze 2020 |
| Rv1758 | R6G |  | Increase | Decrease | Gene frameshift deletion associated with hypervirulence and enhanced growth in macrophage. | Lam et. al., 2011 |
| Rv1883c | V73A |  | Decrease (n = 2) | Increase (n = 2) | Known mutation associated with IR | Lagutkin et. al., 2022 |
| Rv1899c | W12R |  | Decrease | Decrease | No report  |  |
| Rv1907c | D48E |  | Increase (n = 2) | Increase(n = 2) | Gene associated with IR |  Lagutkin et. al., 2022 |
| Rv1997 | G292S | *ctpF M. tuberculosis* cation transporter | Decrease | Decrease | Gene regulated by DosR, involved in hypoxia, dormancy regulon and ion transport | Pulido et. al., 2014 |
| Rv2043c | Q10\* | *pncA,* pyrazinamidase enzyme | Decrease | Increase | Gene involved in Pyrazinamide resistance | Baddam et. al., 2018 |
| Rv2083 | Q126K |  | No change | No change |  |  |
| Rv2318 | G323S |  | No change | No change |  |  |
| Rv2329c | L69F | *narK1* | Increase | Decrease | Gene overexpressed under nitrogen limitation in *M. tuberculosis* | Williams et. al., 2015 |
| Rv2351c | G174R | *plcA* Membrane-associated phospholipase C | Increase | Decrease | Gene displaying high within-host genetic diversity. | Shockey et. al., 2019 |
| I171V | Increase (n = 1)Decrease (n = 1) | Increase (n = 1)No change (n = 1) |
| T168A | Increase (n = 1)Decrease(n = 1) | Increase (n = 1)No change (n = 1) |
| Rv2394 | H347Y | *ggtB*, Oxidative stress proteins | Decrease | Decrease | Gene upregulated in *M. tuberculosis* under oxidative stress induced by sulfamethoxazole | Sarkar et. al., 2018 |
| Rv2398c | L80P | *cysW*,Sulphate transport system permease protein, resuscitation-promoting factor. | Decrease | Increase | Gene upregulated under starvation model of *M. tuberculosis* persistence | Betts et. al., 2002Gorla et. al., 2018 |
| Rv2400c | K342E | *subI* Sulphate binding precursor | Decrease | Increase | * Gene upregulated under starvation model of *M. tuberculosis* persistence
* Possible role in antibiotic tolerance.
 | Betts et. al., 2002Xu et. al., 2017 |
| Rv2488c | I463S | LuxR family regulator  | Increase | Decrease | Gene family involved in *M. tuberculosis* dormancy and virulence | Fang et. al., 2013 |
| Rv2543 | A139T | *IppA* | Decrease | Increase | Regulated by stationary phase sigma factor *sigD* | Calamita et. al., 2005 |
| H37Q | Increase | Decrease |
| N38S | Increase (n = 2) | Increase (n = 1)Decrease(n = 1) |
| Rv2544 | H44R | Membrane lipoprotein | Decrease | Decrease |  | Fleischmann et. al., 2002 |
| P43R | Increase | Increase |
| Rv2545 | L33F | *vapBC* Toxin-antitoxin modules | Decrease | Increase | Regulate bacterial growth arrest. | Ahidjo et. al., 2011 |
| Rv2689c | P335L |  | Decrease | Increase | Gene with mutation during *M. tuberculosis* latent infection | Colangeli et. al., 2014 |
| Rv2728c | P188S | Conserved alanine rich protein | Decrease | Decrease |  | Li et. al., 2015 |
| Rv2836c | G191R | *dinF* | No change | No change | Gene associated with DNA repair and upregulated in pulmonary TB | Rachman et. al., 2006 |
| Rv2893 | V164M | Similar to alkanal monooxygenase alpha chain | No change | No change | Gene repressed in acid stress | Fisher et. al., 2002 |
| Rv3138 | R278H | Pyruvate–formate–lyase activating protein | Increase | Increase | Gene upregulated in *M. tuberculosis* stationary phase | Hampshire et. al., 2004 |
| Rv3424c | V96A |  | Increase (n = 2) | Increase (n = 1)Decrease(n = 1) | Gene displaying high within-host genetic diversity. | Nimmo et. al., 2020 |
| Rv3483c | D191G |  | Increase | Increase | MmpL3 (mycolic acid transporter) interacting protein | Belardinelli et. al., 2019 |
| Rv3680 | N378D |  | Increase(n = 1)No change(n = 1) | Increase(n = 2) | Gene involved in protecting *M. tuberculosis* from Glycerol and Nitric Oxide toxicity | Whitaker et. al., 2020 |
| Rv3758c | F209L | *proV* | Decrease | Increase | Role in the maintenance of osmoregulation within the phagosome | Gautam et. al., 2019 |
| Rv3901c | A38G |  | Increase | No change | Role in virulence of *M. marinum* | Ruley et. al., 2004 |
| T16I | Increase | No change |

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