Coll, F; Phelan, J; Hill-Cawthorne, GA; Nair, MB; Mallard, K; Ali, S; Abdallah, AM; Alghamdi, S; Alsomali, M; Ahmed, AO; Portelli, S; Oppong, Y; Alves, A; Bessa, TB; Campino, S; Caws, M; Chatterjee, A; Crampin, AC; Dheda, K; Furnham, N; Glynn, JR; Grandjean, L; Minh Ha, D; Hasan, R; Hasan, Z; Hibberd, ML; Joloba, M; Jones-Lopez, EC; Matsumoto, T; Miranda, A; Moore, DJ; Mocillo, N; Panaiotov, S; Parkhill, J; Penha, C; Perdigo, J; Portugal, I; Rchiad, Z; Robledo, J; Sheen, P; Shesha, NT; Sirgel, FA; Sola, C; Oliveira Sousa, E; Streicher, EM; Helden, PV; Viveiros, M; Warren, RM; McNerney, R; Pain, A; Clark, TG (2018) Genome-wide analysis of multi- and extensively drug-resistant Mycobacterium tuberculosis. Nature genetics. ISSN 1061-4036 DOI: https://doi.org/10.1038/s41588-017-0029-0

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### Supplementary Table 1

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**Populations contributing to the analysis**

Abbreviations: L1, lineage 1; L2, lineage 2; L3, lineage 3; L4, lineage 4; Susc., susceptible; DR, resistant to at least one drug but not MDR-TB/XDR-TB. Notes: *Bangladesh (8), China (1), Nepal (4), Pakistan (1), Philippines (4), South Korea (39), Thailand (1), Cameroon (1), Central African Republic (1), Equatorial Guinea (1), Guinea (1), Morocco (4), Niger (1), Nigeria (1), Democratic Republic of Congo (4), Rwanda (15), Germany (12), Kazakhstan (1), Portugal (1), Spain (2), Brazil (7), Colombia (1), Dominican Republic (1), Peru (31); **Malaysia, South Africa, and Thailand (96); *** PRJEB10950, PRJEB10385; **** ERP013054, PRJEB10950; ***** PRJNA183624, PRJNA235615, PRJEB10385; ****** PRJEB2221, PRJEB5162, PRJEB6273, PRJEB6276, PRJEB7281, PRJEB7727, PRJEB9680, PRJNA282721; **bolded ENA accession numbers** include sequencing performed as part of the TB Global Drug Resistance Collaboration (http://pathogenseq.lshtm.ac.uk/#tuberculosis).
**Supplementary Table 2**

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**Phenotype**

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**Drugs susceptibility test data (resistant/tested) and the phenotypes considered**

Abbreviations: DR, resistant to at least 1 drug but not MDR-TB/XDR-TB; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensive drug-resistant tuberculosis; PAS Para-amino salicylic acid. Notes: MOX and OFL are fluoroquinolones (FLQ); CAP, KAN and AMK are second-line injectables drugs.
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**Allele frequency of resistance mutations**

Abbreviations: DR, Resistant to at least 1 drug but not MDR-TB/XDR-TB; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis; IGR, intergenic region;

* stop codon
### Supplementary Table 4

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<td>4243217</td>
<td>X or M v SUS, EMB</td>
<td>2.09E-14</td>
<td>0</td>
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<tr>
<td>embC-embA</td>
<td>4243221</td>
<td>X v SUS, EMB</td>
<td>1.70E-32</td>
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<td>0.058</td>
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</tr>
<tr>
<td>embC-embA</td>
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<td>X v SUS, EMB</td>
<td>2.62E-10</td>
<td>0</td>
<td>0.012</td>
<td>0.011</td>
<td>0.040</td>
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<tr>
<td>embB</td>
<td>4247429</td>
<td>M or X v SUS, EMB</td>
<td>1.28E-47</td>
<td>0.001</td>
<td>0.064</td>
<td>0.317</td>
<td>0.401</td>
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</tr>
<tr>
<td>embB</td>
<td>4247431</td>
<td>M or X v SUS, EMB</td>
<td>1.58E-51</td>
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<td>0.062</td>
<td>0.174</td>
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<tr>
<td>embB</td>
<td>4247574</td>
<td>X or M v SUS, EMB</td>
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<td>0.004</td>
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<tr>
<td>embB</td>
<td>4247702</td>
<td>X v SUS, EMB</td>
<td>2.62E-08</td>
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<tr>
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<td>4247729</td>
<td>X or M v SUS, EMB</td>
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<td>0.009</td>
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<tr>
<td>embB</td>
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<td>X v SUS, EMB</td>
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<tr>
<td>embB</td>
<td>4247781</td>
<td>X v SUS</td>
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<tr>
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<td>1.33E-26</td>
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<td>0.017</td>
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<tr>
<td>embB</td>
<td>4249583</td>
<td>X v SUS, EMB</td>
<td>5.84E-23</td>
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<tr>
<td>ubiA</td>
<td>4269271</td>
<td>X v M or SUS</td>
<td>1.01E-16</td>
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<td>0.002</td>
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<tr>
<td>ethA</td>
<td>4326435</td>
<td>X v SUS</td>
<td>3.44E-14</td>
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<tr>
<td>ethA-ethR</td>
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<td>0.025</td>
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</tr>
<tr>
<td>gid</td>
<td>4407965</td>
<td>X v SUS</td>
<td>6.27E-10</td>
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<td>0.021</td>
<td>0.010</td>
<td>0.031</td>
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</tr>
</tbody>
</table>

**Lineage specific SNP associations**

Abbreviations: X, XDR-TB; M, MDR-TB; Susc., Pan susceptible; DR, resistant to at least one drug but not MDR-TB/XDR-TB; RIF, rifampicin; INH, isoniazid; ETH, ethionamide; EMB, ethambutol; KAN, kanamycin.
**Supplementary Table 5**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Resistance gene</th>
<th>Co-occurring gene</th>
<th>Fisher exact test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>rpoB</td>
<td>rpoC*</td>
<td>&lt; 2.2e-16</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>rpoB</td>
<td>rpoA*</td>
<td>6.0e-09</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>katG</td>
<td>ahpC*</td>
<td>&lt; 2.2e-16</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>pncA</td>
<td>pncB2</td>
<td>1.4e-13</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>embB</td>
<td>ubiA</td>
<td>&lt; 2.2e-16</td>
</tr>
<tr>
<td>PAS</td>
<td>thyA</td>
<td>thyX-hsdS.1</td>
<td>&lt; 2.2e-16</td>
</tr>
</tbody>
</table>

**Detected co-occurrence of mutations at drug resistance associated loci (Fisher exact test P<10^-8)**

Abbreviations: PAS, para-aminosalicylic acid. Note: underlying overall and lineage data are presented in Supplementary Table 6; * known compensatory mechanisms
Supplementary Table 6

Co-occurrence of mutations at drug resistance associated loci with a breakdown by lineage

<table>
<thead>
<tr>
<th>Gene</th>
<th>Overall</th>
<th>Lineage 1</th>
<th>Lineage 2</th>
<th>Lineage 3</th>
<th>Lineage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>rpoB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>4964</td>
<td>873</td>
<td>557</td>
<td>30</td>
<td>417</td>
</tr>
<tr>
<td>Mut.</td>
<td>138</td>
<td>477</td>
<td>15</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>rpoC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>5060</td>
<td>1308</td>
<td>564</td>
<td>45</td>
<td>439</td>
</tr>
<tr>
<td>Mut.</td>
<td>43</td>
<td>42</td>
<td>8</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>rpoA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>5066</td>
<td>1308</td>
<td>564</td>
<td>45</td>
<td>439</td>
</tr>
<tr>
<td>Mut.</td>
<td>43</td>
<td>42</td>
<td>8</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>katG</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>4959</td>
<td>1390</td>
<td>554</td>
<td>58</td>
<td>472</td>
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<tr>
<td>Mut.</td>
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<td>62</td>
<td>4</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>ahpC</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>5608</td>
<td>599</td>
<td>560</td>
<td>23</td>
<td>704</td>
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<tr>
<td>Mut.</td>
<td>116</td>
<td>59</td>
<td>24</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>pncA</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>5576</td>
<td>647</td>
<td>528</td>
<td>15</td>
<td>701</td>
</tr>
<tr>
<td>Mut.</td>
<td>147</td>
<td>11</td>
<td>58</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>ethA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>5922</td>
<td>285</td>
<td>541</td>
<td>33</td>
<td>914</td>
</tr>
<tr>
<td>Mut.</td>
<td>143</td>
<td>15</td>
<td>38</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>thyA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>5033</td>
<td>1281</td>
<td>502</td>
<td>91</td>
<td>489</td>
</tr>
<tr>
<td>Mut.</td>
<td>45</td>
<td>104</td>
<td>21</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Co-occurrence of mutations at drug resistance associated loci with a breakdown by lineage

Each table contains the number of isolates with and without mutations ('mutant' (Mut) & 'wild type' (WT) respectively) at each pair of drug resistance associated loci effects identified or known compensatory effects. ‘Mutant’ refers to isolates with SNP and indel non-synonymous amino acid changes. Synonymous amino acid changes and deep phylogenetic mutations were discarded. Cells with grey background show statistically significant correlations (Fisher exact test P<0.02), i.e. pairs of genes frequently mutated in the same isolates, whereas white background indicates lack of statistical significance. This analysis points to putative epistatic and compensatory relationships.
### Supplementary Table 7

<table>
<thead>
<tr>
<th>Genomic position</th>
<th>Mutation</th>
<th>Overall Mutation Frequency</th>
<th>Resist. Freq.</th>
<th>mCSM *</th>
<th>DUET *</th>
<th>mCSM-Lig **</th>
<th>Distance from CYS **</th>
<th>mCSM-PPI ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>3840259</td>
<td>Y388D</td>
<td>0.0009</td>
<td>0</td>
<td>-3.369</td>
<td>-3.384</td>
<td>-3.737</td>
<td>2.682</td>
<td>-2.819</td>
</tr>
<tr>
<td>3840258</td>
<td>Y388C</td>
<td>0.0002</td>
<td>0</td>
<td>-1.889</td>
<td>-1.704</td>
<td>-1.938</td>
<td>2.682</td>
<td>-2.489</td>
</tr>
<tr>
<td>3840393</td>
<td>M343T_B</td>
<td>0.0031</td>
<td>0.0358</td>
<td>-2.118</td>
<td>-2.085</td>
<td>0.368</td>
<td>3.636</td>
<td>-0.195</td>
</tr>
<tr>
<td>3840708</td>
<td>S238L</td>
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<td>0</td>
<td>0.611</td>
<td>1.192</td>
<td>0.69</td>
<td>4.246</td>
<td>-0.551</td>
</tr>
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<td>3840952</td>
<td>K157E</td>
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<td>0</td>
<td>-1.483</td>
<td>-1.455</td>
<td>-1.841</td>
<td>4.474</td>
<td>-0.075</td>
</tr>
<tr>
<td>3840636</td>
<td>P262Q</td>
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<td>0</td>
<td>-2.015</td>
<td>-2.069</td>
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<td>4.987</td>
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<td>-1.460</td>
<td>0.706</td>
<td>5.212</td>
<td>-0.588</td>
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<td>R340L_B</td>
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<tr>
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<td>0</td>
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<td>-1.554</td>
<td>-2.467</td>
<td>6.992</td>
<td>-0.419</td>
</tr>
<tr>
<td>3840639</td>
<td>S261N</td>
<td>0.0002</td>
<td>0</td>
<td>-1.443</td>
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<td>-0.482</td>
<td>7.116</td>
<td>-0.248</td>
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<tr>
<td><strong>3841083</strong></td>
<td><strong>L113R</strong></td>
<td><strong>0.0057</strong></td>
<td><strong>0.4461</strong></td>
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<td><strong>-0.956</strong></td>
<td><strong>-1.721</strong></td>
<td><strong>8.477</strong></td>
<td><strong>-0.423</strong></td>
</tr>
</tbody>
</table>

**Protein structural modelling of alr reveals low frequency mutations conferring higher instability**

We applied four measures to quantify the enthalpic effects (the change in Gibbs free energy - ΔΔG) of point mutations on overall protein structure stability (mCSM and DUET), protein-protein interactions (mCSM-PPI) and interaction with substrate/drug (mCSM-Lig). Negative values indicate a destabilising effect, with the most destabilising highlighted in grey, and positive values indicating an increase in stability. The geometrical distance from the mutation to the drug binding position is also provided. The mutation that was statistically significant with the largest resistance frequency (L113R) has a relatively large destabilising effect both on the overall protein structure and in drug binding, yet it is the furthest from the site of drug interaction. Abbreviations: CY5, D-cycloscerine. Notes: * protein stability; ** drug binding, *** protein-protein interactions; bolded the mutation that was statistically significant; grey – less stability.
### Supplementary Table 8

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>indels/Kb</th>
<th>Total No. positions</th>
<th>Length Median (bp)</th>
<th>Length Range (bp)</th>
<th>Assoc. P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR-TB vs. Susc.</td>
<td>embCAB promoter</td>
<td>72.29</td>
<td>6</td>
<td>1</td>
<td>1-2</td>
<td>8.34E-09</td>
</tr>
<tr>
<td>MDR-TB vs. Susc.</td>
<td>pncA</td>
<td>44.72</td>
<td>25</td>
<td>1</td>
<td>1-15</td>
<td>2.09E-08</td>
</tr>
<tr>
<td>MDR-TB vs. Susc.</td>
<td>rpoB</td>
<td>2.27</td>
<td>7</td>
<td>6</td>
<td>3-9</td>
<td>3.91E-03</td>
</tr>
<tr>
<td>XDR-TB vs. Susc.</td>
<td>ethA</td>
<td>25.89</td>
<td>38</td>
<td>1</td>
<td>1-10</td>
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<td>XDR-TB vs. Susc.</td>
<td>pncA</td>
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<td>25</td>
<td>1</td>
<td>1-15</td>
<td>1.20E-23</td>
</tr>
<tr>
<td>XDR-TB vs. Susc.</td>
<td>rpoB</td>
<td>2.27</td>
<td>7</td>
<td>6</td>
<td>3-9</td>
<td>4.63E-14</td>
</tr>
<tr>
<td>XDR-TB vs. Susc.</td>
<td>embCAB promoter</td>
<td>72.29</td>
<td>6</td>
<td>1</td>
<td>1-2</td>
<td>6.93E-07</td>
</tr>
<tr>
<td>XDR- vs. MDR-TB</td>
<td>pncA</td>
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<td>25</td>
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<td>1-15</td>
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<tr>
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<td>ald</td>
<td>10.77</td>
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<td>1-5</td>
<td>4.85E-04</td>
</tr>
<tr>
<td>XDR- vs. MDR-TB</td>
<td>rrs</td>
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<td>1</td>
<td>1-1</td>
<td>2.71E-03</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>katG</td>
<td>5.40</td>
<td>12</td>
<td>1.5</td>
<td>1-12</td>
<td>2.82E-05</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>rpoB</td>
<td>2.27</td>
<td>7</td>
<td>6</td>
<td>3-9</td>
<td>1.25E-10</td>
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<td>Ethionamide</td>
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<td>7.22E-09</td>
</tr>
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<td>Capreomycin</td>
<td>tlyA</td>
<td>3.73</td>
<td>3</td>
<td>2</td>
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<td>1.21E-12</td>
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<td>Capreomycin</td>
<td>rrs</td>
<td>2.61</td>
<td>4</td>
<td>1</td>
<td>1-1</td>
<td>2.37E-10</td>
</tr>
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<td>1.45E-09</td>
</tr>
<tr>
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<td>25</td>
<td>1</td>
<td>1-15</td>
<td>5.27E-38</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>ald</td>
<td>10.77</td>
<td>12</td>
<td>1</td>
<td>1-5</td>
<td>5.35E-03</td>
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<tr>
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<td>rrs</td>
<td>2.61</td>
<td>4</td>
<td>1</td>
<td>1-1</td>
<td>9.29E-05</td>
</tr>
</tbody>
</table>

**Gene-based small insertion and deletion (indel) associations**

Abbreviations: Susc., susceptible; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.
### Supplementary Table 9

<table>
<thead>
<tr>
<th>Gene</th>
<th>No. samples</th>
<th>Drug</th>
<th>No. DR</th>
<th>No. XDR-TB</th>
<th>Mean size (bp)</th>
<th>Size range (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dfrA/thyA</td>
<td>5</td>
<td>PAS</td>
<td>1</td>
<td>3</td>
<td>6,396</td>
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</tr>
<tr>
<td>pncA</td>
<td>12</td>
<td>PZA</td>
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<tr>
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<td>ETH</td>
<td>3</td>
<td>3</td>
<td>3,667</td>
<td>1,513-5,271</td>
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<td>katG</td>
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<td>INH</td>
<td>3</td>
<td>0</td>
<td>5,729</td>
<td>4,789-7,608</td>
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</tbody>
</table>

**Large deletions in candidate drug resistance regions**

Abbreviations: DR, resistant to at least one drug but not MDR/XDR-TB; XDR-TB, extensively drug-resistant tuberculosis; PAS, para-aminosalicylic acid; ETH, ethionamide; PZA, pyrazinamide; INH, isoniazid.