**Table S1**

The samples according to geographic location and phenotypic drug resistance

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Number of isolates belonging to lineage** | | | | **Number of isolates showing resistance to** | | | | | | | | |
| Source | **Tot.** | **L1** | **L2** | **L3** | **L4** | **SM** | **INH** | **RMP** | **EMB** | **OFL** | **KAN** | **CAP** | **Et** | **PZA** |
| ***Asia*** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bangladesh | 8 | 4 | 1 | 1 | 2 | 2 | 4 | 1 | 4 | 1 | - | - | 1 | - |
| China (Tibet) | 1 | 1 | - | - | - | 1 | 1 | 1 | - | - | - | - | - | - |
| Nepal | 4 | 1 | 2 | - | 1 | 4 | 3 | 2 | 1 | 1 | - | - | - | 2 |
| Pakistan | 1 | - | - | 1 | - | - | - | - | - | - | - | - | - | - |
| Philippines | 4 | 4 | - | - | - | 1 | 2 | 2 | 1 | - | - | - | 2 | - |
| Sth Korea | 39 | - | 23 | 1 | 15 | 17 | 26 | 17 | 15 | - | - | 1 | 1 | 3 |
| Thailand | 1 | - | 1 | - | - | - | - | - | - | 1 | 1 | 1 | - | - |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ***Africa*** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cameroon | 1 | - | - | - | 1 | 1 | - | - | - | - | - | - | - | - |
| CAR | 1 | - | - | - | 1 | - | - | - | - | 1 | - | - | - | - |
| Guinea | 1 | - | - | - | 1 | - | 1 | - | - | - | - | - | - | - |
| Guinea Eq. | 1 | - | - | - | 1 | - | 1 | 1 | - | - | - | - | 1 | - |
| Morocco | 4 | - | - | - | 4 | 2 | 3 | 1 | 1 | - | - | - | - | - |
| Niger | 1 | - | - | - | 1 | - | - | - | - | - | 1 | 1 | - | - |
| Nigeria | 2 | - | - | - | 2 | - | 1 | 1 | - | 1 | - | - | 1 | - |
| RDC | 4 | - | - | - | 4 | - | - | - | - | - | 1 | 1 | - | - |
| Rwanda | 15 | - | - | - | 15 | 4 | 15 | 15 | 10 | - | - | - | 1 | - |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ***Europe*** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Germany | 12 | - | 1 | 1 | 10 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | - | - |
| Kazakhstan | 1 | - | - | - | 1 | - | - | 1 | - | - | - | - | - | - |
| Portugal | 1 | - | - | - | 1 | 1 | 1 | 1 | - | - | - | - | - | - |
| Spain | 2 | - | - | - | 2 | 1 | - | 1 | - | - | - | - | - | - |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ***South America*** | |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Brazil | 7 | - | - | - | 7 | 2 | 4 | 4 | 2 | 1 | - | - | 1 | 1 |
| Colombia | 1 | - | - | - | 1 | - | 1 | 1 | - | - | - | - | - | - |
| Peru | 31 | - | 5 | - | 26 | 9 | 9 | 11 | 6 | 1 | - | 1 | 1 | - |
| Rep. Domin. | 1 | - | - | - | 1 | - | - | - | - | - | - | - | - | - |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Overall** | **144** | **10** | **33** | **4** | **97** | **48** | **73** | **61** | **41** | **8** | **4** | **6** | **9** | **6** |

CAR Central African Republic; DRC Democratic Republic of Congo, L1-L4 lineages 1 to 4, (first line drugs) RMP = Rifampicin, INH = Isoniazid, SM = Streptomycin, EMB = Ethambutol; (second line drugs) OFL = Ofloxacin , KAN = kanamycin, CAP = capreomycin, Et = ethionamide, P =Para-aminosalisylic acid.

**Table S2**

The isolate ENA accession numbers and MIC values

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ENA Accession | TDR Accession | RMP MIC | INH MIC | SM MIC | EMB MIC |
| ERR1213824 | TB-TDR-0070 | >120 | 3.2 | 4 | 8 |
| ERR1213825 | TB-TDR-0073 | >120 | 0.8 | ≤1 | 4 |
| ERR1213826 | TB-TDR-0074 | 80 | 3.2 | 2 | ≤1 |
| ERR1213827 | TB-TDR-0077 | 30 | 0.2 | 2 | ≤1 |
| ERR1213828 | TB-TDR-0078 | ≤10 | 0.2 | ≤1 | 2 |
| ERR1213829 | TB-TDR-0079 | 80 | 0.2 | 4 | ≤1 |
| ERR1213830 | TB-TDR-0080 | ≤10 | 0.2 | ≤1 | ≤1 |
| ERR1213831 | TB-TDR-0081 | ≤10 | 0.2 | ≤1 | 2 |
| ERR1213832 | TB-TDR-0082 | ≤10 | 3.2 | ≤1 | 2 |
| ERR1213833 | TB-TDR-0083 | ≤10 | 3.2 | ≤1 | ≤1 |
| ERR1213834 | TB-TDR-0084 | ≤10 | 3.2 | ≤1 | ≤1 |
| ERR1213835 | TB-TDR-0085 | ≤10 | 3.2 | 8 | 4 |
| ERR1213836 | TB-TDR-0086 | >120 | 0.8 | ≤1 | 2 |
| ERR1213837 | TB-TDR-0087 | >120 | 3.2 | 8 | 4 |
| ERR1213838 | TB-TDR-0088 | >120 | 0.2 | ≤1 | ≤1 |
| ERR1213839 | TB-TDR-0089 | >120 | 0.8 | ≤1 | 8 |
| ERR1213840 | TB-TDR-0090 | >120 | 0.2 | ≤1 | 2 |
| ERR1213841 | TB-TDR-0091 | 20 | 0.2 | 2 | 2 |
| ERR1213842 | TB-TDR-0092 | ≤10 | 0.2 | 2 | 4 |
| ERR1213843 | TB-TDR-0093 | ≤10 | >3.2 | 8 | 4 |
| ERR1213844 | TB-TDR-0094 | ≤10 | 0.2 | ≤1 | 8 |
| ERR1213845 | TB-TDR-0095 | ≤10 | 0.8 | >16 | ≤1 |
| ERR1213846 | TB-TDR-0096 | ≤10 | ≤0.05 | >16 | ≤1 |
| ERR1213847 | TB-TDR-0097 | 30 | 0.2 | >16 | ≤1 |
| ERR1213848 | TB-TDR-0098 | 40 | 0.2 | 16 | 2 |
| ERR1213849 | TB-TDR-0099 | >120 | >3.2 | 4 | >8 |
| ERR1213850 | TB-TDR-0101 | 80 | 3.2 | 2 | 4 |
| ERR1213851 | TB-TDR-0102 | >120 | 3.2 | ≤1 | 2 |
| ERR1213852 | TB-TDR-0104 | ≤10 | >3.2 | ≤1 | 4 |
| ERR1213853 | TB-TDR-0106 | >120 | 3.2 | ≤1 | 2 |
| ERR1213854 | TB-TDR-0108 | ≤10 | 0.8 | 8 | ≤1 |
| ERR1213855 | TB-TDR-0109 | ≤10 | 3.2 | >16 | 2 |
| ERR1213856 | TB-TDR-0110 | ≤10 | >3.2 | >16 | 2 |
| ERR1213857 | TB-TDR-0112 | >120 | 0.8 | >16 | ≤1 |
| ERR1213858 | TB-TDR-0113 | 120 | >3.2 | >16 | 4 |
| ERR1213859 | TB-TDR-0116 | 80 | >3.2 | 8 | >8 |
| ERR1213860 | TB-TDR-0117 | >120 | >3.2 | ≤1 | 2 |
| ERR1213861 | TB-TDR-0119 | >120 | 3.2 | 4 | ≤1 |
| ERR1213862 | TB-TDR-0120 | 30 | >3.2 | 16 | 4 |
| ERR1213863 | TB-TDR-0122 | >120 | 3.2 | >16 | 4 |
| ERR1213864 | TB-TDR-0123 | 20 | >3.2 | >16 | 8 |
| ERR1213865 | TB-TDR-0124 | >120 | >3.2 | >16 | 4 |
| ERR1213866 | TB-TDR-0125 | >120 | 0.2 | ≤1 | 2 |
| ERR1213867 | TB-TDR-0126 | ≤10 | 0.2 | 2 | ≤1 |
| ERR1213868 | TB-TDR-0129 | >120 | 1.6 | 2 | ≤1 |
| ERR1213869 | TB-TDR-0130 | ≤10 | ≤0.05 | 2 | ≤1 |
| ERR1213870 | TB-TDR-0131 | >120 | >3.2 | >16 | ≤1 |
| ERR1213871 | TB-TDR-0132 | ≤10 | >3.2 | 4 | 4 |
| ERR1213872 | TB-TDR-0133 | >120 | 1.6 | 8 | 4 |
| ERR1213873 | TB-TDR-0134 | >120 | >3.2 | 4 | ≤1 |
| ERR1213874 | TB-TDR-0135 | >120 | >3.2 | ≤1 | >8 |
| ERR1213875 | TB-TDR-0136 | ≤10 | ≤0.05 | 2 | ≤1 |
| ERR1213876 | TB-TDR-0137 | ≤10 | ≤0.05 | 2 | ≤1 |
| ERR1213877 | TB-TDR-0138 | ≤10 | ≤0.05 | 2 | 2 |
| ERR1213878 | TB-TDR-0139 | ≤10 | 0.2 | 2 | 2 |
| ERR1213879 | TB-TDR-0140 | ≤10 | 0.2 | ≤1 | ≤1 |
| ERR1213880 | TB-TDR-0141 | >120 | 0.2 | >16 | ≤1 |
| ERR1213881 | TB-TDR-0142 | 20 | 0.2 | 2 | 2 |
| ERR1213882 | TB-TDR-0143 | ≤10 | 0.2 | 16 | 2 |
| ERR1213883 | TB-TDR-0144 | ≤10 | >3.2 | >16 | 4 |
| ERR1213884 | TB-TDR-0146 | 40 | 0.2 | 8 | ≤1 |
| ERR1213885 | TB-TDR-0147 | 20 | >3.2 | >16 | ≤1 |
| ERR1213886 | TB-TDR-0148 | >120 | >3.2 | >16 | 2 |
| ERR1213887 | TB-TDR-0149 | >120 | >3.2 | >16 | 4 |
| ERR1213888 | TB-TDR-0150 | >120 | 1.6 | 2 | ≤1 |
| ERR1213889 | TB-TDR-0152 | 120 | 3.2 | 8 | 8 |
| ERR1213890 | TB-TDR-0153 | 80 | 3.2 | 4 | 2 |
| ERR1213891 | TB-TDR-0155 | 120 | >3.2 | 2 | 2 |
| ERR1213892 | TB-TDR-0156 | ≤10 | 0.2 | 2 | 4 |
| ERR1213893 | TB-TDR-0157 | >120 | 0.2 | >16 | 2 |
| ERR1213894 | TB-TDR-0158 | ≤10 | ≤0.05 | 2 | ≤1 |
| ERR1213895 | TB-TDR-0159 | ≤10 | ≤0.05 | 2 | ≤1 |
| ERR1213896 | TB-TDR-0160 | 80 | 0.2 | 8 | ≤1 |
| ERR1213897 | TB-TDR-0161 | ≤10 | ≤0.05 | ≤1 | ≤1 |
| ERR1213898 | TB-TDR-0163 | ≤10 | ≤0.05 | ≤1 | ≤1 |
| ERR1213899 | TB-TDR-0164 | ≤10 | ≤0.05 | 8 | ≤1 |
| ERR1213900 | TB-TDR-0165 | >120 | 0.2 | 2 | ≤1 |
| ERR1213901 | TB-TDR-0166 | >120 | 3.2 | >16 | 2 |
| ERR1213902 | TB-TDR-0167 | >120 | 3.2 | 16 | 4 |
| ERR1213903 | TB-TDR-0169 | ≤10 | ≤0.05 | >16 | ≤1 |
| ERR1213904 | TB-TDR-0170 | >120 | >3.2 | 2 | 4 |
| ERR1213905 | TB-TDR-0171 | >120 | 0.2 | ≤1 | ≤1 |
| ERR1213906 | TB-TDR-0172 | 20 | >3.2 | 2 | ≤1 |
| ERR1213907 | TB-TDR-0173 | ≤10 | ≤0.05 | ≤1 | ≤1 |
| ERR1213908 | TB-TDR-0174 | ≤10 | ≤0.05 | 2 | ≤1 |
| ERR1213909 | TB-TDR-0175 | >120 | 0.8 | ≤1 | 4 |
| ERR1213910 | TB-TDR-0176 | >120 | 1.6 | >16 | 2 |
| ERR1213911 | TB-TDR-0177 | 20 | 0.2 | 2 | ≤1 |
| ERR1213912 | TB-TDR-0178 | ≤10 | 0.8 | 2 | ≤1 |
| ERR1213913 | TB-TDR-0180 | ≤10 | 0.2 | 2 | ≤1 |
| ERR1213914 | TB-TDR-0181 | ≤10 | ≤0.05 | 8 | 2 |
| ERR1213915 | TB-TDR-0182 | 20 | ≤0.05 | >16 | ≤1 |
| ERR1213916 | TB-TDR-0183 | >120 | 0.8 | 2 | ≤1 |
| ERR1213917 | TB-TDR-0184 | ≤10 | ≤0.05 | 2 | ≤1 |
| ERR1213918 | TB-TDR-0185 | >120 | 0.8 | 2 | ≤1 |
| ERR1213919 | TB-TDR-0186 | >120 | >3.2 | ≤1 | ≤1 |
| ERR1213920 | TB-TDR-0187 | ≤10 | >3.2 | 8 | 2 |
| ERR1213921 | TB-TDR-0189 | >120 | >3.2 | 8 | ≤1 |
| ERR1213922 | TB-TDR-0190 | >120 | ≤0.05 | >16 | ≤1 |
| ERR1213923 | TB-TDR-0191 | >120 | >3.2 | 8 | 8 |
| ERR1213924 | TB-TDR-0193 | >120 | >3.2 | >16 | 2 |
| ERR1213925 | TB-TDR-0194 | 20 | 0.2 | 2 | ≤1 |
| ERR1213926 | TB-TDR-0195 | 20 | 3.2 | 2 | 8 |
| ERR1213927 | TB-TDR-0197 | 20 | 0.2 | ≤1 | 2 |
| ERR1213928 | TB-TDR-0198 | >120 | 3.2 | 8 | 4 |
| ERR1213929 | TB-TDR-0199 | ≤10 | 0.2 | ≤1 | 2 |
| ERR1213930 | TB-TDR-0200 | ≤10 | ≤0.05 | ≤1 | ≤1 |
| ERR1213931 | TB-TDR-0201 | >120 | >3.2 | 16 | ≤1 |
| ERR1213932 | TB-TDR-0202 | 20 | ≤0.05 | 4 | 2 |
| ERR1213933 | TB-TDR-0203 | ≤10 | ≤0.05 | 2 | ≤1 |
| ERR1213934 | TB-TDR-0204 | 20 | ≤0.05 | 4 | ≤1 |
| ERR1213935 | TB-TDR-0207 | ≤10 | ≤0.05 | 2 | ≤1 |
| ERR1213936 | TB-TDR-0208 | 20 | 0.2 | ≤1 | ≤1 |
| ERR1213937 | TB-TDR-0209 | 20 | 0.2 | 2 | ≤1 |
| ERR1213938 | TB-TDR-0210 | 20 | ≤0.05 | ≤1 | ≤1 |
| ERR1213939 | TB-TDR-0213 | 20 | 0.8 | 2 | ≤1 |
| ERR1213940 | TB-TDR-0214 | ≤10 | ≤0.05 | 2 | ≤1 |
| ERR1213941 | TB-TDR-0016 | ≤10 | 0.2 | ≤1 | 2 |
| ERR1213942 | TB-TDR-0017 | ≤10 | 0.2 | 2 | ≤1 |
| ERR1213943 | TB-TDR-0018 | >120 | 0.2 | ≤1 | ≤1 |
| ERR1213944 | TB-TDR-0022 | 20 | ≤0.05 | 2 | ≤1 |
| ERR1213945 | TB-TDR-0038 | ≤10 | >3.2 | >16 | ≤1 |
| ERR1213946 | TB-TDR-0041 | ≤10 | ≤0.05 | 2 | ≤1 |
| ERR1213947 | TB-TDR-0042 | ≤10 | >3.2 | ≤1 | >8 |
| ERR1213948 | TB-TDR-0043 | 20 | 3.2 | ≤1 | 8 |
| ERR1213949 | TB-TDR-0045 | ≤10 | 0.2 | 2 | 4 |
| ERR1213950 | TB-TDR-0007 | >120 | >3.2 | >16 | 4 |

RMP rifampicin, INH isoniazid, SM streptomycin, EMB ethambutol

**Table S3**

Drug susceptibility profiles for rifampicin, isoniazid, streptomycin and ethambutol

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| No. samples | Rifampicin | Isoniazid | Streptomycin | Ethambutol |
| *12 (9.4%)* | ***R*** | ***R*** | ***R*** | ***R*** |
| *8 (6.3%)* | ***R*** | ***R*** | ***R*** | *S* |
| *8 (6.3%)* | ***R*** | ***R*** | *S* | ***R*** |
| *14 (11.0%)* | ***R*** | ***R*** | *S* | *S* |
| 4 (3.1%) | **R** | S | **R** | S |
| 7 (5.5%) | **R** | S | S | S |
| 5 (3.4%) | S | **R** | **R** | **R** |
| 7 (5.5%) | S | **R** | **R** | S |
| 5 (3.4%) | S | **R** | S | **R** |
| 6 (4.7%) | S | **R** | S | S |
| 9 (7.1%) | S | S | **R** | **S** |
| 4 (3.1%) | S | S | S | **R** |
| 38 (29.9%) | S | S | S | S |

R = resistance, S = sensitive; 13 different profiles were identified across 127 independent samples; Multi-drug resistant in italics

**Table S4**

Combinations of mutations and their frequency (N) in drug resistance candidate genes

a) Rifampicin

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Mutation observed in *rpoB* codons | | | | | | | | | | *rpoC* | N | MIC (µg/ml) | | |
| 45 | 170 | 250 | 400 | 435 | 445 | 4  5  0 | 491 | 692 | rare |  |  | Mean | Min | Max |
|  |  |  |  |  |  |  |  |  |  |  | 70 | 15.3 | 10.0 | 80.0 |
|  |  |  |  |  |  |  |  |  | \* |  | 5 | 68.0 | 10.0 | 120.0 |
|  |  |  |  |  |  |  |  | \* |  |  | 1 | 10.0 | 10.0 | 10.0 |
|  |  |  |  |  |  |  | \* |  |  |  | 1 | 80.0 | 80.0 | 80.0 |
|  |  |  |  |  |  | \* |  |  |  |  | 21 | 114.3 | 80.0 | 120.0 |
|  |  |  |  |  |  | \* |  |  |  | \* | 1 | 120.0 | 120.0 | 120.0 |
|  |  |  |  |  |  | \* |  |  | \* |  | 2 | 120.0 | 120.0 | 120.0 |
|  |  |  |  |  |  | \* |  |  | \* | \* | 1 | 120.0 | 120.0 | 120.0 |
|  |  |  |  |  |  | \* | \* |  |  |  | 1 | 120.0 | 120.0 | 120.0 |
|  |  |  |  |  |  | \*\* |  |  |  |  | 1 | 120.0 | 120.0 | 120.0 |
|  |  |  |  |  | \* |  |  |  |  |  | 9 | 120.0 | 120.0 | 120.0 |
|  |  |  |  | \* |  |  |  |  |  |  | 4 | 120.0 | 120.0 | 120.0 |
|  |  |  |  | \* |  |  |  | \* |  |  | 1 | 120.0 | 120.0 | 120.0 |
|  |  |  | \* |  |  | \* |  |  |  |  | 2 | 120.0 | 120.0 | 120.0 |
|  |  | \* |  |  |  |  |  |  |  |  | 2 | 10.0 | 10.0 | 10.0 |
|  | \* |  |  |  |  |  |  |  |  |  | 1 | 120.0 | 120.0 | 120.0 |
|  | \* |  |  |  |  |  |  |  | \* |  | 1 | 120.0 | 120.0 | 120.0 |
| \* |  |  |  |  |  | \* |  |  |  |  | 3 | 120.0 | 120.0 | 120.0 |

b) Isoniazid

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| *katG* codons | | | *inhA*  prom. | N | MIC (µg/ml) | | |
| 315 | 436 | rare |  |  | Mean | Min | Max |
|  |  |  |  | 46 | 0.3 | 0.05 | 3.2 |
|  |  | \* |  | 2 | 0.2 | 0.2 | 0.2 |
|  |  | \*\*\* |  | 1 | 3.2 | 3.2 | 3.2 |
|  |  |  | \* | 8 | 1.7 | 0.8 | 3.2 |
|  |  | \* | \* | 1 | 1.6 | 1.6 | 1.6 |
| \* |  |  |  | 23 | 2.9 | 0.2 | 3.2 |
| \* |  | \* |  | 1 | 3.2 | 3.2 | 3.2 |
| \* |  |  | \* | 2 | 3.2 | 3.2 | 3.2 |
|  | \* |  |  | 18 | 0.2 | 0.05 | 0.8 |
|  | \* |  | \* | 4 | 1.0 | 0.8 | 1.6 |
|  | \* | \* | \* | 1 | 3.2 | 3.2 | 3.2 |
| \* | \* |  |  | 18 | 3.2 | 3.2 | 3.2 |
| \* | \* | \* |  | 1 | 3.2 | 3.2 | 3.2 |
| \* | \* |  | \* | 1 | 3.2 | 3.2 | 3.2 |

**c)** Streptomycin

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| *rpsL* codons | | *rrs* | N | MIC (µg/ml) | | |
| 43 | 88 |  |  | Mean | Min | Max |
|  |  |  | 99 | 3.8 | 1 | 16 |
|  |  | \* | 13 | 10.0.4 | 1 | 16 |
|  | \* |  | 4 | 16.0 | 16 | 16 |
| \* |  |  | 11 | 16.0 | 16 | 16 |

**d)** Ethambutol

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *embB* codons | | | | | |  |  |  | *ubiA* | *embA* | N | MIC (µg/ml) | | |
| 297 | 306 | 319 | 354 | 378 | 406 | 497 | 1024 | r  a  r  e |  |  |  | Mean | Min | Max |
|  |  |  |  |  |  |  |  |  |  |  | 70 | 1.2 | 1 | 2 |
|  |  |  |  |  |  |  |  |  |  | \*\* | 1 | 4.0 | 4 | 4 |
|  |  |  |  |  |  |  |  |  | \* |  | 2 | 1.5 | 1 | 2 |
|  |  |  |  |  |  |  |  |  | \*\* |  | 1 | 1.0 | 1 | 1 |
|  |  |  |  |  |  |  |  | \* |  |  | 3 | 1.7 | 1 | 2 |
|  |  |  |  |  |  |  |  | \*\* |  |  | 1 | 2.0 | 2 | 2 |
|  |  |  |  |  |  |  | \* |  |  |  | 1 | 4.0 | 4 | 4 |
|  |  |  |  |  |  | \* |  |  |  |  | 5 | 4.8 | 4 | 8 |
|  |  |  |  |  |  | \* |  |  | \* |  | 1 | 4.0 | 4 | 4 |
|  |  |  |  |  | \* |  |  |  |  |  | 6 | 4.5 | 1 | 8 |
|  |  |  |  |  | \* |  |  |  | \* |  | 4 | 2.8 | 1 | 4 |
|  |  |  |  |  | \* |  | \* |  |  |  | 1 | 4.0 | 4 | 4 |
|  |  |  |  |  | \* |  | \* | \* |  |  | 1 | 4.0 | 4 | 4 |
|  |  |  |  | \* |  |  |  |  | \*\* |  | 3 | 1.0 | 1 | 1 |
|  |  |  |  | \* |  | \* |  | \* | \*\* |  | 1 | 2.0 | 2 | 2 |
|  |  |  | \* |  |  |  |  |  |  | \* | 1 | 4.0 | 4 | 4 |
|  |  |  | \* | \* |  |  |  |  | \*\* |  | 1 | 4.0 | 4 | 4 |
|  |  |  | \* | \* |  |  |  | \* | \*\* |  | 1 | 4.0 | 4 | 4 |
|  |  | \* |  |  |  |  |  |  |  |  | 3 | 4.7 | 2 | 8 |
|  | \* |  |  |  |  |  |  |  |  |  | 11 | 4.1 | 1 | 8 |
|  | \* |  |  |  |  |  |  |  |  | \* | 1 | 4.0 | 4 | 4 |
|  | \* |  |  |  |  |  |  |  | \* |  | 1 | 8.0 | 8 | 8 |
|  | \* |  |  |  |  |  |  | \* |  |  | 1 | 2.0 | 2 | 2 |
|  | \* |  |  | \* |  |  |  |  | \*\* |  | 2 | 8.0 | 8 | 8 |
|  | \* |  | \* |  |  |  |  |  |  |  | 1 | 8.0 | 8 | 8 |
| \* |  |  |  |  |  |  |  |  |  |  | 2 | 2.5 | 1 | 4 |
| \* |  |  |  |  |  |  |  |  |  | \* | 1 | 8.0 | 8 | 8 |

\* single mulation, \*\* double mutations, \*\*\* triple mutations; SNP mutations in a single sample have been aggregated into a “rare” column.

**Table S5**

Predicted effects of mutations

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Gene | Mutation | Distance to interface (Å) | Distance to ligand (Å) | DUET (ΔΔG kcal/mol) | mCSM-Stability (ΔΔG kcal/mol) | SDM (ΔΔG kcal/mol) |
| *rpoB* | T400A |  | 42.914 | 0.031 | -0.326 | 2.480 |
| D435V |  | 3.094 | 0.336 | 0.356 | 1.860 |
| H445D |  | 4.015 | -2.084 | -1.971 | -1.730 |
| H445Y |  | 4.015 | -0.214 | -0.171 | -0.310 |
| H445R |  | 4.015 | -1.958 | -1.857 | -1.950 |
| S450W |  | 5.773 | -0.756 | -0.840 | 2.330 |
| S450L |  | 5.773 | 0.102 | -0.126 | 2.820 |
| I491V |  | 2.908 | -1.221 | -1.274 | -0.830 |
| I491F |  | 2.908 | -1.529 | -1.416 | -0.760 |
| *katG* | S315N | 14.940 | 2.149 | -0.100 | -0.184 | 2.149 |
| S315T | 14.940 | 2.149 | -0.243 | -0.330 | 2.149 |