## Supplementary methods.

### Isolates with bedaquiline and linezolid resistance

The isolates analysed in the study were from our previous reports (Zimenkov, 2017, Peretokina, 2019, Ushtanit, 2020). Isolates were obtained from patients who received bedaquiline and linezolid as the core drugs during treatment. All isolates were investigated by phenotypic bedaquiline susceptibility testing on Middlebrook 7H11 agar and Bactec MGIT 960 liquid media. Resistance to linezolid (Sigma-Aldrich Co., St. Louis, MO, USA) resistance was determined using a MGIT 960 (critical concentration of 1mg/L).

|  |  |  |
| --- | --- | --- |
| Patient Iq | *rv0678* – t274ta\*AtpE – G25S\* D28G\* | MIC Bdq:0.25 mg/L (agar) 1 mg/L (liquid) |
| Patient Jk | AtpE – A63L (gca🡪tta) | MIC Bdq:>1 mg/L (agar) 4 mg/L (liquid) |
| Patient Bg | RplC – C154R (tgt🡪cgt\*/agg\*) | Lzd - R |

\* - heteroresistant state.

Whole genome sequencing was additionally performed for isolates from patients Iq and Bg. The isolate from patient Jk was sequenced previously (Ushtanit, 2020, accession SRR16168839).

Genomic DNA was extracted using the Gentra Puregene Yeast/Bact. Kit (QIAGEN cat no. 158567). Briefly, 0.25 mL of culture suspension aliquots were centrifuged at 13500 rpm for 5 min. The pellet was washed and treated with Puregene cell lysis buffer and Proteinase K. The DNA was washed with ethanol and resuspended using a a hydration solution. The DNA concentration was measured with a Qubit HS DNA fluorometer (Life Technologies, Carlsbad, CA, USA). Whole genome sequencing was performed using the MiniSeq platform (Illumina, San Diego, CA, USA).

Sequencing data in FastQ format was analysed using the internal pipeline. The reads were trimmed using the Trimmomatic tool (Bolger, 2014), mapped to the reference genome of *M. tuberculosis* (GenBank accession NC\_000962.3) (Cole, 1998) with BWA-MEM (Li, 2010) and refined using BamLeftAlign [59]. Variant calling was performed using FreeBayes (Garrison, 2012) and filtered with the VCFlib toolkit. Variant annotation was performed using SnpEff (Cingolani, 2012).

The raw sequencing data was submitted to the Sequence Read Archive of the National Centre for Biotechnology Information (accession number PRJNA768108).

### CRyPTIC database retrieval and analysis

Molecular and phenotypic data were obtained from the official CRyPRTIC FTP server [http://ftp.ebi.ac.uk/pub/ databases/cryptic/](http://ftp.ebi.ac.uk/pub/%20databases/cryptic/). The following files were downloaded from the subdirectory /release\_june2022/reproducibility/data\_tables/cryptic-analysis-group (accessed on July, 2023):

* VARIANTS.csv, containing data on nucleotide mutations,
* MUTATIONS.csv, containing data on amino acid substitutions and codon changes, and
* CRyPTIC\_reuse\_table\_20211019.csv, which contained phenotypic data for 12288 isolates.

Data processing and analysis was performed using custom Python scripts. First, all amino acid substitutions and SNPs for 12288 isolates were extracted from the VARIANTS and MUTATIONS tables into separate tables.

Highly repetitive PE/PPE genes, insertion elements, and phages were excluded from the analysis. The 3680 genes of total length 3.62 Mbases comprised 82% of *M. tuberculosis* H37Rv genome (NC\_000962.3).

Two thousand three hundred and eighty-eight isolates were excluded from the study due to the presence of mixed and unknown mutations marked as ‘x’ or ‘o’ in the annotation. Mutations of the final set of 9941 isolates were remapped onto *M. canetti* genome (NC\_015848.1). The list of amino acid substitutions was used to build the Python *numpy* and *gmpy2* tables with binary data on the presence of particular substitutions for all isolates.

The phylogenetic tree was built using the Nearest-Neighbout approach (Saitou, 1987) and the MEGA 11 software (Tamura, 2021). The robustness of tree was checked using lineage-specific SNPs (Coll, 2014). Isolates belonged to four main lineages – Indo-Oceanic (L1), East-African-Indian (L3), East-Asian (L2), and Euro-American (L4) (Figure S1).

Each genomic mutation was mapped to the phylogeny using parsimony approach. First, the lists of nearest neighbours and descendants for each terminal branch corresponding to isolate were obtained. If some mutation was absent in the analyzing isolate, but were present in the neighbours and ancestors, we supposed that the both the common and reverse mutation occurred in this case, and the list of mutations was updated to include these two steps in the analyzed isolate. The same approach was used for the same gene and codon mutation of different type – such mutations were splitted into common ancestral mutation plus change from ancestral to isolate-specific mutation (Figure S1).

These corrections of mutation lists allowed to map mutations along the phylogenetic tree and identify the nodes where mutation emerged. The initial frequencies of mutations (number of isolates with mutations) were corrected to number of nodes with mutations, which is drastaclly lower for the most of mutations (Table S2). In total, 325,419 different mutations were found in this set of isolates. The initial and phylogeny-adjusted numbers of mutation events in population were equal to 42,379,768 and 449,223, respectively. Adjusted frequencies of 3-nucleotide substitutions in one codon and dinucleotide substitutions, leading to synonymous amino acid substitutions (Arg, Leu, Ser), were as alow as 42 and 97, and were omitted from the analysis.

For the statistical analysis of mutational events the Fisher exact test was used as in widely used GWAS approach, also designated as dN/dS and branch-site test (Farhat, 2013; Chiner-Oms, 2022; Liu, 2022). Breakpoint values of *p*-values (-log10P-value) were selected on the basis of Bonferroni correction, three deviations from the the expected value using the analysis of distributions, or QQ-plotting (Taboga, 2021). The most strict values were used.

Three main values were analyzed – the conventional ratio of nonsynonymous to synonymous substitutions dN/dS, ratio of dinucleotide to single-nucleotude nonsynonymous substitutions d2N/d1N, and ratio of dinucleotide to synonymous substitutions d2N/dS. The results of the latter two approaches had a greater priority for the further analysis, particularly in the case if the mutation event was insignificant by dN/dS approach.

Both source frequencies (number of isolates with and without the mutation) and phylogeny-adjusted frequencies were used in several statistical calculations.

First, source frequencies were splitted based on resistance profile of the isolates and associations of mutations of different types with resistance were analyzed by conventional Fisher exact test. From the whole set of isolates 3695 were resistant to at least rifampicin, and 5429 to any of the drugs analysed by CRYpTIC consortium (rifampicin, rifabutin, isoniazid, moxifloxacin, levofloxacin, ethambutol, ethionamide, kanamycin, amikacin, clofazimine, bedaquiline, linezolid, delamanid). Manhattan plots of dN/dS, d2N/d1N, and d2N/dS derived values are shown on Figure S2.

Another approach was based on pairwise comparison of mutation frequencies in different genes with normalization per gene length. To construct the matrix of -log10(P-values) for each pair of genes dN and dS values for gene *i* were compared to dN and dS values of the gene *j*. Average values for each gene were calculated at each row of the matrix and plotted (Figure S3).Two calculations were performed using initial and phylogeny-adjusted numbers of mutations (allele and homoplasy counting).

The fourth approach was the estimation of the difference between phylogenetically adjusted mutational events and expected values at the level of individual codon. To obtain the null hypothesis for comparison the codon substitution matrix (20 x 20) was obtained from the total number of phylogeny-adjusted codon substitution events (n=449,223). Then, for each codon expected values of synonymous, non-synonymous caused by single- and dinucleotide substitutions were estimated from the matrix using Monte-Carlo method. Number of events were balanced with the total number of observed mutations in particular codon. For simplification of data presentation, maximal *p*-values for each gene are provided on Manhattan plot (Figure S4) and in a table format (Table S3).

### Correction of annotation

In the article by Koch et al., 2017, cited in the Section 2.3, the annotation of mutation in *cyp138* gene was not correct due to the simultaneous presence of two SNVs in one codon. They annotated c163705t as P114S, while the correct substitution is cc163705tt, leading to amino acid substitution P114F. Genomes from this study were partially reanalyzed, and at least the following genomes with accessions ERR1633777, ERR1633797 have both SNVs.

ERR1633775, ERR1633776, ERR1633778, ERR1633779, ERR1633780, ERR1633781, ERR1633782, ERR1633783, ERR1633784, ERR1633785, ERR1633786, ERR1633787, ERR1633788, ERR1633789, ERR1633790, ERR1633791, ERR1633792, ERR1633793, ERR1633794, ERR1633795, ERR1633796 were wild-type.

### Neisseria genomes analysis

The set of *Neisseria gonorrhoeae* genomes were analyzed using the same pipeline as used for *M. tuberculosis*. The raw SRA files (*n*=1,164) from the study by Grad et al. (Grad, 2014) were downloaded and aligned on the reference genome *N. gonorrhoeae* NCCP11945 (NC\_011035.1) with BWA-MEM. The sequence of *N. lactamica* ATCC 23970 (SRR2906934) was used as a root for the phylogenetic analysis. Calculation of distances, bulding of the phylogenetic tree, parsimony and statistical analysis were performed as described above.

In the total set 64,574 single- and 707 (1.1%) dinucleotide substitutions were found. In total, 15 genes with statistically significant frequency of 2N mutations were identified (Table S3).

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## Figure S1.

Phylogenetic tree of the 9941 genomes that were sequenced and analyzed by the CRYpTIC Consortium obtained by Nearest-Neighbour method rooted onto *M. canetii* (**A**). Main *M. tuberculosis* lineages are shown with different colors. Lineage 6 and animal-adapted strains (*M. tuberculosis var. bovis, var. orygis*) are tightly bound and comprise the most ancient branch. Sublineages were mapped onto the tree using the SNP lists from Coll, 2014 and Thawornwattana, 2021. The unadjusted distribution of isolates with substitutions are shown with color along the whole set of isolates.



## Figure S2

Pairwise analysis of 2N vs. 1N substitution statistics for *M. tuberculosis* and *N. gonorrhoeae* sets of isolates. P-values for dN/dS are plotted on *x* axis, d2N/dS – on *y* axis. Statistical significance borderline with Bonferroni correction are shown as red dotted lines.



## Table S1.

RpoB substitutions and rifampicin resistance phenotype.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Amino acid substitution | Wild-type codon | Mutated codon | Resistant isolates with mutation | Total number of resistan isolates in the study | Susceptible isolates with mutation | Total number of susceptible isolates in the study |  Study |
| V170F | gtc | ttc | 35 | 71 |  |  | (Walker et al. 2022) |
| V170F | gtc | ttc | 3 | 3 | 0 | 3 | (Heep et al. 2000) |
| V170F | gtc | unkn. | 1 | 36 | 0 | 5 | (Jamieson et al. 2014) |
| V170F | gtc | unkn. | 5 | 871 | 0 | 6139 | (Zignol et al. 2018) |
| V170F | gtc | unkn. | 6 | 14 |  |  | (Solari, Santos-Lazaro, and Puyen 2020) |
| V170F | gtc | ttc | 2 | 324 | 0 | 28 | (Vargas et al. 2020) |
| V170G | gtc | ggc | 0 | 0 | 0 | 0 | (Walker et al. 2022) |
| V170A | gtc | gcc | 0 | 8 | 0 | 1 | (Walker et al. 2022) |
| Q172K | cag | aag | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| Q172R | cag | cgg | 0 | 7 | 0 | 0 | (Walker et al. 2022) |
| H194Y | cac | tac | 1 | 1 | 12 | 12 | (Walker et al. 2022) |
| H194R | cac | unkn. | 1 | 14 |  |  | (Solari, Santos-Lazaro, and Puyen 2020) |
| E250G | gag | ggg | 1 | 9 | 70 | 89 | (Walker et al. 2022) |
| E250G | gag | unkn. | 1 | 14 |  |  | (Solari, Santos-Lazaro, and Puyen 2020) |
| E250G | gag | ggg | 1 | 324 | 3 | 28 | (Vargas et al. 2020) |
| A286V | gcg | gtg | 0 | 41 | 0 | 0 | (Walker et al. 2022) |
| A286V | gcg | gtg | 1 | 21 | 0 | 19 | (Taniguchi et al. 1996) |
| Q409H | cag | cat | 1 | 41 |  |  | (Cavusoglu et al. 2002) |
| Q409R | cag | cgg | 0 | 38 | 0 | 0 | (Walker et al. 2022) |
| E423A | gag | gcg | 2 | 105 |  |  | (Schilke et al. 1999) |
| E423A | gag | gcg | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| E423G | gag | ggg | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| F424L | ttc | ctc | 0 | 4 | 0 | 0 | (Walker et al. 2022) |
| F424L | ttc | ttg | 2 | 13 | 0 | 26 | (Heym et al. 1994) |
| F424L | ttc | tta | 2 | 13 | 0 | 26 | (Stavrum et al. 2009) |
| F424L | ttc | ttg | 0 | 2 | 0 | 0 | (Walker et al. 2022) |
| F424S | ttc | tcc | 1 | 112 | 0 | 30 | (Wang et al. 2007) |
| F424V | ttc | gtc | 0 | 16 | 0 | 0 | (Walker et al. 2022) |
| F424C | ttc | tgc | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| G426S | ggc | agc | 1 | 41 | 0 | 245 | (Sandgren et al. 2009) |
| G426S | ggc | agc | 0 | 0 | 1 | 1 | (Walker et al. 2022) |
| G426D | ggc | gac | 1 | 32 | 0 | 26 | (Kim et al. 1997) |
| G426D | ggc | gat | 2 | 41 | 0 | 245 | (Sandgren et al. 2009) |
| G426G | ggc | ggt | 0 | 0 | 0 | 1 | (Walker et al. 2022) |
| T427G | acc | ggc | 0 | 0 | 1 | 1 | (Walker et al. 2022) |
| T427H | acc | cac | 6 | 41 | 0 | 245 | (Sandgren et al. 2009) |
| T427P | acc | ccc | 4 | 41 | 0 | 245 | (Sandgren et al. 2009) |
| T427A | acc | gcc | 2 | 41 | 0 | 245 | (Sandgren et al. 2009) |
| T427A | acc | gcc | 0 | 2 | 1 | 1 | (Walker et al. 2022) |
| T427I | acc | atc | 0 | 4 | 0 | 0 | (Walker et al. 2022) |
| T427N | acc | aac | 0 | 0 | 1 | 1 | (Walker et al. 2022) |
| T427S | acc | agc | 1 | 44 | 0 | 6 | (Sandgren et al. 2009) |
| T427S | acc | agc | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| T427S | acc | gct | 1 | 17 | 0 | 0 | (Sandgren et al. 2009) |
| T427T | acc | act | 0 | 0 | 0 | 2 | (Walker et al. 2022) |
| S428G | agc | ggc | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| S428Q | agc | cag | 1 | 15 | 0 | 10 | (Sandgren et al. 2009) |
| S428T | agc | acc | 0 | 3 | 0 | 0 | (Walker et al. 2022) |
| S428T | agc | acc | 1 | 108 | 0 | 12 | (Sandgren et al. 2009) |
| S428T | agc | unkn. | n.d. | 1302 | 1 |  | (Mvelase et al. 2019) |
| S428R | agc | agg | 0 | 28 | 1 | 110 | (Sandgren et al. 2009) |
| S428R | agc | cgc | 0 | 2 | 0 | 0 | (Walker et al. 2022) |
| S428R | agc | agg | 0 | 0 | 0 | 0 | (Walker et al. 2022) |
| S428R | agc | cgc | 1 | 57 | 0 |  | (ElMaraachli et al. 2015) |
| S428I | agc | atc | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| S428S | agc | agt | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| Q429H | cag | cac | 2 | 64 | 0 | 49 | (Sandgren et al. 2009) |
| Q429H | cag | cat | 0 | 2 | 0 | 0 | (Walker et al. 2022) |
| Q429H | cag | cac | 0 | 4 | 0 | 1 | (Walker et al. 2022) |
| Q429P | cag | unkn. | 1 | 36 | 0 | 0 | (Sirgel et al. 2013) |
| Q429P | cag | ccg | 0 | 0 | 0 | 0 | (Walker et al. 2022) |
| Q429K | cag | aag | 1 | 15 | 0 | 10 | (Sandgren et al. 2009) |
| Q429L | cag | ctg | 0 | 9 | 0 | 0 | (Walker et al. 2022) |
| L430P | ctg | unkn. | 2 | 66 | 0 | 56 | (Telenti et al. 1993) |
| L430P | ctg | ccg | 4 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| L430P | ctg | ccg | 1 | 36 | 0 | 10 | (Bodmer et al. 1995) |
| L430P | ctg | ccg | 3 | 109 | 0 |  | (Wang et al. 2007) |
| L430P | ctg | unkn. | 1 | 300 | 2 | 315 | (Van Deun et al. 2013) |
| L430P | ctg | ccg | 0 | 36 | 2 | 5 | (Jamieson et al. 2014) |
| L430P | ctg | ccg | 0 | 102 | 3 | 62 | (Berrada et al. 2016) |
| L430P | ctg | ccg | 2 | 256 | 0 |  | (Jing et al. 2017) |
| L430P | ctg | unkn. | 3 | 139 | 1 | 17 | (Miotto et al. 2018) |
| L430P | ctg | unkn. | 10 | 871 | 20 | 6139 | (Zignol et al. 2018) |
| L430P | ctg | unkn. | n.d. | 1302 | 7 |  | (Mvelase et al. 2019) |
| L430P | ctg | ccg | 4 |  | 7 |  | (Torrea et al. 2019) |
| L430P | ctg | ccg | 31 | 106 | 96 | 103 | (Walker et al. 2022) |
| L430P | ctg | ccg | 0 | 153 | 1 | 9 | (Campbell et al. 2011) |
| L430R | ctg | cgg | 2 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| L430R | ctg | cgg | 0 | 21 | 0 | 1 | (Walker et al. 2022) |
| L430V | ctg | gtg | 2 | 94 | 0 | 32 | (Sandgren et al. 2009) |
| L430V | ctg | unkn. | 0 | 300 | 1 | 315 | (Van Deun et al. 2013) |
| L430Q | ctg | unkn. | 1 | 139 | 0 | 17 | (Miotto et al. 2018) |
| S431T | agc | acc | 1 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| S431T | agc | acc | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| S431R |  agc | unkn. | 1 | 139 | 0 | 17 | (Miotto et al. 2018) |
| S431R | agc | cgc | 1 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| S431R | agc | cgc | 0 | 2 | 0 | 0 | (Walker et al. 2022) |
| S431R | agc | aga | 0 | 0 | 0 | 0 | (Walker et al. 2022) |
| S431I | agc | atc | 1 | 64 | 0 | 49 | (Sandgren et al. 2009) |
| S431G | agc | ggc | 0 | 6 | 0 | 0 | (Walker et al. 2022) |
| Q432E | caa | gaa | 2 | 102 | 0 | 62 | (Berrada et al. 2016) |
| Q432E | caa | gaa | 1 | 154 | 0 | 113 | (Sandgren et al. 2009) |
| Q432E | caa | gaa | 1 | 139 | 0 | 17 | (Miotto et al. 2018) |
| Q432E | caa | gaa | 1 | 154 |  |  | (Matsui et al. 2020) |
| Q432E | caa | gaa | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| Q432H | caa | cac | 1 | 82 | 0 | 18 | (Sandgren et al. 2009) |
| Q432H | caa | cac | 0 | 2 | 0 | 0 | (Walker et al. 2022) |
| Q432H | caa | cat | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| Q432K | caa | aaa | 1 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| Q432K | caa | aaa | 3 | 102 | 0 | 62 | (Berrada et al. 2016) |
| Q432K | caa | aaa | 1 | 49 | 0 | 114 | (Otchere et al. 2016) |
| Q432K | caa | aaa | 1 | 139 | 0 | 17 | (Miotto et al. 2018) |
| Q432K | caa | aaa | 4 | 336 | 0 | 55 | (Rodwell et al. 2014) |
| Q432K | caa | aaa | 4 | 57 |  |  | (ElMaraachli et al. 2015) |
| Q432K | caa | aaa | 2 | 871 | 1 | 6139 | (Zignol et al. 2018) |
| Q432K | caa | aaa | 18 | 34 | 1 | 1 | (Walker et al. 2022) |
| Q432L | caa | unkn. | 2 | 66 | 0 | 56 | (Telenti et al. 1993) |
| Q432L | caa | cta | 1 | 36 | 0 | 10 | (Bodmer et al. 1995) |
| Q432L | caa | cta | 1 | 10 | 0 |  | (Zaczek et al. 2009) |
| Q432L | caa | cta | 2 | 300 | 0 | 315 | (Van Deun et al. 2013) |
| Q432L | caa | cta | 2 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| Q432L | caa | cta | 1 | 102 | 0 | 62 | (Berrada et al. 2016) |
| Q432L | caa | cta | 4 | 139 | 0 | 17 | (Miotto et al. 2018) |
| Q432L | caa | cta | 1 | 871 | 0 | 6139 | (Zignol et al. 2018) |
| Q432L | caa | unkn. | 1 | 52 |  |  | (Suthum, Samosornsuk, and Samosornsuk 2020) |
| Q432L | caa | cta | 16 | 21 | 1 | 1 | (Walker et al. 2022) |
| Q432L | caa | cta | 1 | 153 | 0 | 9 | (Campbell et al. 2011) |
| Q432N | caa | aat | 2 | 41 | 0 | 245 | (Sandgren et al. 2009) |
| Q432N | caa | aac | 1 | 256 | 0 |  | (Jing et al. 2017) |
| Q432N | caa | aat | 1 | 1 | 0 | 0 | (Walker et al. 2022) |
| Q432P | caa | cca | 1 | 41 |  |  | (Cavusoglu et al. 2002) |
| Q432P | caa | cca | 2 | 109 | 0 |  | (Wang et al. 2007) |
| Q432P | caa | cca | 2 | 300 | 0 | 315 | (Van Deun et al. 2013) |
| Q432P | caa | cca | 2 | 32 | 0 | 26 | (Sandgren et al. 2009) |
| Q432P | caa | cca | 2 | 102 | 0 | 62 | (Berrada et al. 2016) |
| Q432P | caa | cca | 1 | 49 | 0 | 114 | (Otchere et al. 2016) |
| Q432P | caa | cca | 6 | 139 | 0 | 17 | (Miotto et al. 2018) |
| Q432P | caa | cca | 2 | 871 | 0 | 6139 | (Zignol et al. 2018) |
| Q432P |  caa | unkn. | n.d. | 1302 | 21 |  | (Mvelase et al. 2019) |
| Q432P | caa | cca | 1 | 324 | 0 | 28 | (Vargas et al. 2020) |
| Q432P | caa | cca | 20 | 29 | 0 | 1 | (Walker et al. 2022) |
| Q432Q | caa | unkn. | 1 | 139 | 0 | 17 | (Miotto et al. 2018) |
| Q432R | caa | cga |  |  |  |  | (Sandgren et al. 2009) |
| F433F | ttc | ttt | 0 | 102 | 2 | 62 | (Berrada et al. 2016) |
| F433F | ttc | ttt | 0 | 0 | 0 | 13 | (Walker et al. 2022) |
| F433L | ttc | ttg | 1 | 21 | 0 | 18 | (Sandgren et al. 2009) |
| F433V | ttc | gtc | 1 | 82 | 0 | 18 | (Sandgren et al. 2009) |
| M434I | atg | att | 1 | 3 | 1 | 0 | (Walker et al. 2022) |
| M434I | atg | ata |  |  |  |  | (Sandgren et al. 2009) |
| M434I | atg | ata | 1 | 8 | 1 | 2 | (Walker et al. 2022) |
| M434I | atg | atc | 1 | 5 | 1 | 1 | (Walker et al. 2022) |
| M434L | atg | ttg | 0 | 0 | 0 | 1 | (Walker et al. 2022) |
| M434V | atg | unkn. |  |  | 1 |  | (Yang et al. 1998) |
| M434V | atg | gtg | 0 | 4 | 0 | 3 | (Walker et al. 2022) |
| D435A | gac | gcc | 1 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| D435A | gac | gcc | 1 | 84 | 0 | 36 | (Kambli et al. 2015)  |
| D435A | gac | gcc | 0 | 6 | 1 | 2 | (Walker et al. 2022) |
| D435A | gac | gcc | 1 | 153 | 0 | 9 | (Campbell et al. 2011) |
| D435E | gac | gag | 1 | 163 |  |  | (Yang et al. 1998) |
| D435E | gac | gag | 2 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| D435E | gac | gag | 0 | 2 | 0 | 0 | (Walker et al. 2022) |
| D435E | gac | gaa | 0 | 3 | 0 | 0 | (Walker et al. 2022) |
| D435F | gac | unkn. | 3 | 300 | 0 | 315 | (Van Deun et al. 2013) |
| D435F | gac | ttc | 1 | 84 | 0 | 36 | (Kambli et al. 2015) |
| D435F | gac | ttc | 1 | 102 | 0 | 62 | (Berrada et al. 2016) |
| D435F | gac | ttc | 4 | 871 | 0 | 6139 | (Zignol et al. 2018) |
| D435F | gac | ttc | 3 | 324 | 2 | 28 | (Vargas et al. 2020) |
| D435F | gac | ttc | 35 | 39 | 3 | 3 | (Walker et al. 2022) |
| D435G | gac | ggc | 3 | 109 | 0 |  | (Wang et al. 2007) |
| D435G | gac | ggc | 2 | 256 | 0 |  | (Jing et al. 2017) |
| D435G | gac | ggc | 2 | 871 | 0 | 6139 | (Zignol et al. 2018) |
| D435G | gac | ggc | 5 | 76 | 6 | 9 | (Walker et al. 2022) |
| D435H | gac | cac | 3 | 41 | 0 | 245 | (Sandgren et al. 2009) |
| D435H | gac | cac | 0 | 3 | 0 | 0 | (Walker et al. 2022) |
| D435I | gac | atc | 1 | 154 |  |  | (Matsui et al. 2020) |
| D435L | gac | unkn. | 1 | 139 | 0 | 17 | (Miotto et al. 2018) |
| D435L | gac | ctc | 2 | 2 | 0 | 0 | (Walker et al. 2022) |
| D435N | gac | aac | 1 | 105 | 0 | 0 | (Sandgren et al. 2009) |
| D435S | gac | unkn. | 4 | 36 |  |  | (Sirgel et al. 2013) |
| D435T | gac | unkn. | 1 | 36 |  |  | (Sirgel et al. 2013) |
| D435T | gac | acc | 4 | 69 |  |  | (Madania et al. 2012) |
| D435V | gac | unkn. | 6 | 66 | 0 | 56 | (Telenti et al. 1993) |
| D435V | gac | gtc | 1 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| D435V | gac | gtc | 1 | 13 | 0 | 39 | (Heym et al. 1994) |
| D435V | gac | gtc | 3 | 36 | 0 | 10 | (Bodmer et al. 1995) |
| D435V | gac | gtc | 29 | 36 |  |  | (Sirgel et al. 2013) |
| D435V | gac | gtc | 18 | 102 | 0 | 62 | (Berrada et al. 2016) |
| D435V | gac | gtc | 1 | 10 | 0 |  | (Zaczek et al. 2009) |
| D435V | gac | gtc | 14 | 300 | 0 | 315 | (Van Deun et al. 2013) |
| D435V | gac | gtc | 3 | 84 | 0 | 36 | (Kambli et al. 2015) |
| D435V | gac | gtc | 3 |  | 0 |  | (Nosova et al. 2016) |
| D435V | gac | gtc | 1 | 139 | 0 | 17 | (Miotto et al. 2018) |
| D435V | gac | gtc | 2 | 163 |  |  | (Yang et al. 1998) |
| D435V | gac | gtc | 1 | 163 |  |  | (Yang et al. 1998) |
| D435V | gac | gtc | 1 | 163 |  |  | (Yang et al. 1998) |
| D435V | gac | gtc | 2 | 109 | 0 |  | (Wang et al. 2007) |
| D435V | gac | gtc | 23 | 336 | 0 | 55 | (Rodwell et al. 2014) |
| D435V | gac | gtc | 3 | 36 | 0 | 5 | (Jamieson et al. 2014) |
| D435V | gac | gtc | 15 | 57 |  |  | (ElMaraachli et al. 2015) |
| D435V | gac | gtc | 17 | 189 |  |  | (Rukasha et al. 2016) |
| D435V | gac | gtc | 11 | 49 | 0 | 114 | (Otchere et al. 2016) |
| D435V | gac | gtc | 5 | 256 | 0 |  | (Jing et al. 2017) |
| D435V | gac | unkn. | 30 | 871 | 5 | 6139 | (Zignol et al. 2018) |
| D435V | gac | unkn. | n.d. | 1302 | 16 |  | (Mvelase et al. 2019) |
| D435V | gac | unkn. | 1 | 52 |  |  | (Suthum, Samosornsuk, and Samosornsuk 2020) |
| D435V | gac | gtc | 1 | 154 |  |  | (Matsui et al. 2020) |
| D435V | gac | gtc | 67 | 324 | 3 | 28 | (Vargas et al. 2020) |
| D435V | gac | gtc | 706 | 732 | 8 | 9 | (Walker et al. 2022) |
| D435V | gac | gtc | 11 | 153 | 0 | 9 | (Campbell et al. 2011) |
| D435V | gac | gtc | 4 | 69 |  |  | (Madania et al. 2012) |
| D435Y | gac | tac | 2 | 36 | 0 | 10 | (Bodmer et al. 1995) |
| D435Y | gac | tac | 2 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| D435Y | gac | tac | 1 | 109 | 0 |  | (Wang et al. 2007) |
| D435Y | gac | tac | 1 | 10 | 0 |  | (Zaczek et al. 2009) |
| D435Y | gac | tac | 7 | 300 | 1 | 315 | (Van Deun et al. 2013) |
| D435Y | gac | tac | 0 | 0 | 1 | 4 | (Williamson et al. 2012) |
| D435Y | gac | tac | 0 | 336 | 4 | 55 | (Rodwell et al. 2014) |
| D435Y | gac | tac | 3 | 84 | 0 | 36 | (Kambli et al. 2015) |
| D435Y | gac | tac | 0 | 57 | 2 |  | (ElMaraachli et al. 2015) |
| D435Y | gac | tac | 0 |  | 2 |  | (Nosova et al. 2016) |
| D435Y | gac | tac | 0 | 102 | 4 | 62 | (Berrada et al. 2016) |
| D435Y | gac | tac | 1 | 49 | 0 | 114 | (Otchere et al. 2016) |
| D435Y | gac | tac | 1 | 256 | 0 |  | (Jing et al. 2017) |
| D435Y | gac | tac | 5 | 139 | 3 | 17 | (Miotto et al. 2018) |
| D435Y | gac | tac | 12 | 871 | 12 | 6139 | (Zignol et al. 2018) |
| D435Y | gac | tac | 7 |  | 3 |  | (Torrea et al. 2019) |
| D435Y | gac | unkn. | n.d. | 1302 | 11 |  | (Mvelase et al. 2019) |
| D435Y | gac | tac | 2 | 154 |  |  | (Matsui et al. 2020) |
| D435Y | gac | tac | 63 | 162 | 37 | 44 | (Walker et al. 2022) |
| D435Y | gac | tac | 2 | 153 | 0 | 9 | (Campbell et al. 2011) |
| Q436Q | cag | caa | 2 | 57 |  |  | (ElMaraachli et al. 2015) |
| Q436N | cag | aac | 0 | 0 | 0 | 1 | (Walker et al. 2022) |
| Q436P | cag | ccg | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| N437D | aac | gac | 0 | 13 | 0 | 2 | (Walker et al. 2022) |
| N437H | aac | cac | 1 | 32 | 0 | 26 | (Sandgren et al. 2009) |
| N437H | aac | cac | 0 | 3 | 0 | 0 | (Walker et al. 2022) |
| N437I | aac | atc | 1 | 103 | 0 | 10 | (Sandgren et al. 2009) |
| N437I | aac | atc | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| N437S | aac | agc | 0 | 2 | 0 | 1 | (Walker et al. 2022) |
| N437T | aac | acc | 6 | 94 | 0 | 32 | (Sandgren et al. 2009) |
| N437Y | aac | tac | 1 | 112 | 0 | 0 | (Sandgren et al. 2009) |
| N437Y | aac | tac | 0 | 0 | 0 | 1 | (Walker et al. 2022) |
| N438K | aac | aag | 2 | 41 | 0 | 245 | (Sandgren et al. 2009) |
| L440L | ctg | ttg | 1 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| L440L | ctg | ctt | 0 | 0 | 0 | 4 | (Walker et al. 2022) |
| L440M | ctg | atg | 1 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| L440P | ctg | ccg | 0 | 21 | 1 | 18 | (Sandgren et al. 2009) |
| S441A | tcg | gcg | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| S441L | tcg | ttg | 1 | 6+6 | 0 | 56 | (Telenti et al. 1993) |
| S441L | tcg | unkn. | 1 | 36 | 0 | 10 | (Bodmer et al. 1995) |
| S441L | tcg | unkn. | 1 | 300 | 0 | 315 | (Van Deun et al. 2013) |
| S441L | tcg | ttg | 7 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| S441L | tcg | ttg | 2 | 336 | 0 | 55 | (Rodwell et al. 2014) |
| S441L | tcg | ttg | 3 | 36 | 0 | 5 | (Jamieson et al. 2014) |
| S441L | tcg | ttg | 1 | 57 | 0 |  | (ElMaraachli et al. 2015) |
| S441L | tcg | ttg | 1 | 102 | 0 | 62 | (Berrada et al. 2016) |
| S441L | tcg | ttg | 1 | 49 | 0 | 114 | (Otchere et al. 2016) |
| S441L | tcg | ttg | 1 | 256 | 0 |  | (Jing et al. 2017) |
| S441L | tcg | ttg | 1 | 871 | 1 | 6139 | (Zignol et al. 2018) |
| S441L | tcg | ttg | 1 | 154 |  |  | (Matsui et al. 2020) |
| S441L | tcg | ttg | 16 | 26 | 0 | 0 | (Walker et al. 2022) |
| S441M | tcg | atg | 2 | 2 | 0 | 0 | (Walker et al. 2022) |
| S441Q | tcg | unkn. | 8 | 300 | 0 | 315 | (Van Deun et al. 2013) |
| S441Q | tcg | cag | 2 | 33 | 0 | 17 | (Sandgren et al. 2009) |
| S441Q | tcg | cag | 1 | 256 | 0 |  | (Jing et al. 2017) |
| S441Q | tcg | unkn. | 3 | 139 | 0 | 17 | (Miotto et al. 2018) |
| S441Q | tcg | unkn. | 1 | 871 | 0 | 6139 | (Zignol et al. 2018) |
| S441Q | tcg | cag | 11 | 11 | 0 | 0 | (Walker et al. 2022) |
| S441Q | tcg | cag | 2 | 153 | 0 | 9 | (Campbell et al. 2011) |
| S441V | tcg | gtg | 2 | 2 | 0 | 0 | (Walker et al. 2022) |
| S441W | tcg | tgg |  |  |  |  | (Sandgren et al. 2009) |
| S441W | tcg | unkn. | 2 | 139 | 0 | 17 | (Miotto et al. 2018) |
| S441W | tcg | tgg | 1 | 41 |  |  | (Cavusoglu et al. 2002) |
| S441W | tcg | tgg | 1 | 41 |  |  | (Cavusoglu et al. 2002) |
| S441P | tcg | ccg | 3 | 109 | 0 |  | (Wang et al. 2007) |
| G442A | ggg | gcg | 3 | 41 | 0 | 286 | (Bahrmand et al. 2009) |
| G442E | ggg | gag | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| G442W | ccc | acc | 1 | 101 | 0 | 21 | (Sandgren et al. 2009) |
| G442W | ggg | tgg | 1 | 37 | 0 | 0 | (Sandgren et al. 2009) |
| L443L | ttg | ttt | 0 | 2 | 1 | 1 | (Walker et al. 2022) |
| L443S | ttg | tcg | 1 | 15 | 0 | 10 | (Sandgren et al. 2009) |
| L443L | ttg | ctg | 0 | 0 | 0 | 1 | (Walker et al. 2022) |
| L443W | ttg | tgg | 1 | 82 | 0 | 18 | (Sandgren et al. 2009) |
| T444I | acc | atc | 1 | 37 | 0 | 0 | (Sandgren et al. 2009) |
| T444I | acc | atc | 0 | 2 | 0 | 0 | (Walker et al. 2022) |
| T444P | acc | ccc | 1 | 82 | 0 | 18 | (Sandgren et al. 2009) |
| T444S | acc | agc | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| T444T | acc | act | 0 | 0 | 0 | 1 | (Walker et al. 2022) |
| T444T | acc | acg | 0 | 4 | 0 | 0 | (Walker et al. 2022) |
| H445A | cac | gcc | 1 | 102 | 0 | 62 | (Berrada et al. 2016) |
| H445C | cac | tgc | 2 | 32 |  | 26 | (Sandgren et al. 2009) |
| H445C | cac | tgc | 0 | 41 | 1 |  | (Cavusoglu et al. 2002) |
| H445C | cac | tgc | 1 | 84 | 0 | 36 | (Kambli et al. 2015) |
| H445C | cac | tgc | 2 | 102 | 0 | 62 | (Berrada et al. 2016) |
| H445C | cac | tgc | 2 | 49 | 0 | 114 | (Otchere et al. 2016) |
| H445C | cac | tgc | 7 | 256 | 0 |  | (Jing et al. 2017) |
| H445C | cac | tgc | 3 | 139 | 0 | 17 | (Miotto et al. 2018) |
| H445C | cac | tgc | 1 | 871 | 0 | 6139 | (Zignol et al. 2018) |
| H445C | cac | tgc | 2 | 154 |  |  | (Matsui et al. 2020) |
| H445C | cac | tgc | 2 | 324 | 0 | 28 | (Vargas et al. 2020) |
| H445C | cac | tgc | 32 | 36 | 3 | 3 | (Walker et al. 2022) |
| H445C | cac | tgc | 1 | 69 |  |  | (Madania et al. 2012) |
| H445D | cac | unkn. | 5 | 66 | 0 | 56 | (Telenti et al. 1993) |
| H445D | cac | gac | 3 | 36 | 0 | 10 | (Bodmer et al. 1995) |
| H445D | cac | gac | 7 | 109 | 0 |  | (Wang et al. 2007) |
| H445D | cac | gac | 15 | 300 | 0 | 315 | (Van Deun et al. 2013) |
| H445D | cac | gac | 8 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| H445D | cac | gac | 7 | 84 | 0 | 36 | (Kambli et al. 2015) |
| H445D | cac | gac | 1 | 10 | 0 |  | (Zaczek et al. 2009) |
| H445D | cac | gac | 1 |  | 0 |  | (Nosova et al. 2016) |
| H445D | cac | gac | 3 | 102 | 0 | 62 | (Berrada et al. 2016) |
| H445D | cac | gac | 3 | 139 | 0 | 17 | (Miotto et al. 2018) |
| H445D | cac | gac | 1 |  |  |  | (Springer et al. 2009) |
| H445D | cac | gac | 1 | 41 |  |  | (Cavusoglu et al. 2002) |
| H445D | cac | gac | 3 | 336 | 0 | 55 | (Rodwell et al. 2014) |
| H445D | cac | gac | 1 | 36 | 0 | 5 | (Jamieson et al. 2014) |
| H445D | cac | gac | 2 | 57 | 0 |  | (ElMaraachli et al. 2015) |
| H445D | cac | gac | 2 | 49 | 0 | 114 | (Otchere et al. 2016) |
| H445D | cac | gac | 19 | 189 |  |  | (Rukasha et al. 2016) |
| H445D | cac | gac | 11 | 256 | 0 |  | (Jing et al. 2017) |
| H445D | cac | gac | 1 | 256 | 0 |  | (Jing et al. 2017) |
| H445D | cac | gac | 46 | 871 | 4 | 6139 | (Zignol et al. 2018) |
| H445D | cac | unkn. | 1 | 52 |  |  | (Suthum, Samosornsuk, and Samosornsuk 2020) |
| H445D | cac | gac | 1 | 154 |  |  | (Matsui et al. 2020) |
| H445D | cac | gac | 7 | 324 | 0 | 28 | (Vargas et al. 2020) |
| H445D | cac | gac | 275 | 288 | 3 | 3 | (Walker et al. 2022) |
| H445D | cac | gac | 4 | 153 | 0 | 9 | (Campbell et al. 2011) |
| H445D | cac | gac | 4 | 69 |  |  | (Madania et al. 2012) |
| H445F | cac | ttc |  |  |  |  | (Bostanabad et al. 2007) |
| H445F | cac | ttc | 2 | 41 | 0 | 245 | (Sandgren et al. 2009) |
| H445F | cac | ttc | 1 | 871 | 0 | 6139 | (Zignol et al. 2018) |
| H445F | cac | ttc | 1 | 1 | 0 | 0 | (Walker et al. 2022) |
| H445G | cac | ggc | 3 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| H445G | cac | ggc | 1 | 163 |  |  | (Yang et al. 1998) |
| H445G | cac | ggc | 1 | 102 | 0 | 62 | (Berrada et al. 2016) |
| H445G | cac | ggc | 4 | 7 | 3 | 3 | (Walker et al. 2022) |
| H445G | cac | ggc | 1 | 153 | 0 | 9 | (Campbell et al. 2011) |
| H445G | cac | ggc | 1 | 69 |  |  | (Madania et al. 2012) |
| H445L | cac | unkn. | 8 | 300 | 0 | 315 | (Van Deun et al. 2013) |
| H445L | cac | ctg | 1 | 82 | 0 | 18 | (Sandgren et al. 2009) |
| H445L | cac | unkn. | 18 | 871 | 4 | 6139 | (Zignol et al. 2018) |
| H445L | cac | ctc | 105 | 115 | 8 | 8 | (Walker et al. 2022) |
| H445L | cac | ctc | 2 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| H445L | cac | ctc | 1 | 163 |  |  | (Yang et al. 1998) |
| H445L | cac | ctc | 11 | 109 | 0 |  | (Wang et al. 2007) |
| H445L | cac | ctc | 0 | 0 | 1 | 4 | (Williamson et al. 2012) |
| H445L | cac | ctc | 1 | 336 | 3 | 55 | (Rodwell et al. 2014) |
| H445L | cac | ctc | 1 | 36 | 1 | 5 | (Jamieson et al. 2014) |
| H445L | cac | ctc | 1 | 57 | 1 |  | (ElMaraachli et al. 2015) |
| H445L | cac | ctc | 1 |  | 1 |  | (Nosova et al. 2016) |
| H445L | cac | ctc | 1 | 189 |  |  | (Rukasha et al. 2016) |
| H445L | cac | ctc | 4 | 102 | 0 | 62 | (Berrada et al. 2016) |
| H445L | cac | ctc | 6 | 256 | 0 |  | (Jing et al. 2017) |
| H445L | cac | unkn. | n.d. | 1302 | 6 |  | (Mvelase et al. 2019) |
| H445L | cac | ctc | 5 | 154 |  |  | (Matsui et al. 2020) |
| H445L | cac | ctc | 2 | 324 | 0 | 28 | (Vargas et al. 2020) |
| H445L | cac | ctc | 3 | 153 | 2 | 9 | (Campbell et al. 2011) |
| H445L | cac | ctt | 1 | 49 | 0 | 7 | (Sandgren et al. 2009) |
| H445L | cac | unkn. | 7 | 139 | 2 | 17 | (Miotto et al. 2018) |
| H445N | cac | unkn. | 1 | 66 | 0 | 56 | (Telenti et al. 1993) |
| H445N | cac | aac | 3 | 109 | 0 |  | (Wang et al. 2007) |
| H445N | cac | aac | 3 | 46 | 0 | 286 | (Bahrmand et al. 2009) |
| H445N | cac | aac | 0 | 336 | 1 | 55 | (Rodwell et al. 2014) |
| H445N | cac | aac | 2 | 300 | 2 | 315 | (Van Deun et al. 2013) |
| H445N | cac | aac | 1 | 37 | 0 | 13 | (Sandgren et al. 2009) |
| H445N | cac | unkn. | 0 | 36 | 1 | 5 | (Jamieson et al. 2014) |
| H445N | cac | aac | 3 | 84 | 0 | 36 | (Kambli et al. 2015)  |
| H445N | cac | aac | 0 |  | 1 |  | (Nosova et al. 2016) |
| H445N | cac | aac | 0 | 102 | 3 | 62 | (Berrada et al. 2016) |
| H445N | cac | aac | 4 | 256 | 0 |  | (Jing et al. 2017) |
| H445N | cac | unkn. | 4 | 139 | 3 | 17 | (Miotto et al. 2018) |
| H445N | cac | aac | 4 | 871 | 6 | 6139 | (Zignol et al. 2018) |
| H445N | cac | unkn. | 1 | 52 |  |  | (Suthum, Samosornsuk, and Samosornsuk 2020) |
| H445N | cac | aac | 1 | 154 |  |  | (Matsui et al. 2020) |
| H445N | cac | aac | 12 | 46 | 38 | 39 | (Walker et al. 2022) |
| H445N | cac | aac | 0 | 153 | 4 | 9 | (Campbell et al. 2011) |
| H445P | cac | unkn. | 1 | 66 | 0 | 56 | (Telenti et al. 1993) |
| H445P | cac | ccc | 2 | 26 |  | 10 | (Sandgren et al. 2009) |
| H445P | cac | ccc | 2 | 36 | 0 | 10 | (Bodmer et al. 1995) |
| H445P | cac | ccc | 1 | 189 |  |  | (Rukasha et al. 2016) |
| H445P | cac | ccc | 1 |  | 0 |  | (Nosova et al. 2016) |
| H445P | cac | unkn. | 2 | 139 | 0 | 17 | (Miotto et al. 2018) |
| H445P | cac | unkn. | 1 | 52 |  |  | (Suthum, Samosornsuk, and Samosornsuk 2020) |
| H445P | cac | ccc | 2 | 5 | 0 | 0 | (Walker et al. 2022) |
| H445Q | cac | cag | 2 | 26 | 0 | 10 | (Sandgren et al. 2009) |
| H445Q | cac | cag | 0 | 10 | 1 | 1 | (Walker et al. 2022) |
| H445Q | cac | caa | 1 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| H445Q | cac | caa | 0 | 6 | 1 | 0 | (Walker et al. 2022) |
| H445Q | cac | unkn. | 5 | 139 | 0 | 17 | (Miotto et al. 2018) |
| H445R | cac | unkn. | 2 | 66 | 0 | 56 | (Telenti et al. 1993) |
| H445R | cac | cgc | 1 | 32 |  | 26 | (Sandgren et al. 2009) |
| H445R | cac | cgc | 2 | 36 | 0 | 10 | (Bodmer et al. 1995) |
| H445R | cac | cgc | 4 | 41 |  |  | (Cavusoglu et al. 2002) |
| H445R | cac | cgc | 4 | 109 | 0 |  | (Wang et al. 2007) |
| H445R | cac | cgc | 6 | 336 | 0 | 55 | (Rodwell et al. 2014) |
| H445R | cac | cgc | 5 | 300 | 0 | 315 | (Van Deun et al. 2013) |
| H445R | cac | cgc | 2 | 57 | 0 |  | (ElMaraachli et al. 2015) |
| H445R | cac | cgc | 1 | 84 | 0 | 36 | (Kambli et al. 2015) |
| H445R | cac | cgc | 2 | 102 | 0 | 62 | (Berrada et al. 2016) |
| H445R | cac | cgc | 3 |  | 0 |  | (Nosova et al. 2016) |
| H445R | cac | cgc | 2 | 49 | 0 | 114 | (Otchere et al. 2016) |
| H445R | cac | cgc | 1 | 189 |  |  | (Rukasha et al. 2016) |
| H445R | cac | cgc | 9 | 256 | 0 |  | (Jing et al. 2017) |
| H445R | cac | unkn. | 5 | 139 | 0 | 17 | (Miotto et al. 2018) |
| H445R | cac | cgc | 14 | 871 | 1 | 6139 | (Zignol et al. 2018) |
| H445R | cac | unkn. | n.d. | 1302 | 1 |  | (Mvelase et al. 2019) |
| H445R | cac | cgc | 1 | 154 |  |  | (Matsui et al. 2020) |
| H445R | cac | cgc | 64 | 79 | 2 | 2 | (Walker et al. 2022) |
| H445R | cac | cgc | 3 | 153 | 0 | 9 | (Campbell et al. 2011) |
| H445S | cac | agc | 0 | 102 | 2 | 62 | (Berrada et al. 2016) |
| H445S | cac | tcc | 0 | 102 | 1 | 62 | (Berrada et al. 2016) |
| H445S | cac | agc | 1 | 154 |  |  | (Sandgren et al. 2009) |
| H445S | cac | unkn. | 0 | 871 | 2 | 6139 | (Zignol et al. 2018) |
| H445S | cac | unkn. | 3 | 139 | 4 | 17 | (Miotto et al. 2018) |
| H445S | cac | unkn. | n.d. | 1302 | 2 |  | (Mvelase et al. 2019) |
| H425S | cac | tcc | 6 | 14 | 2 | 4 | (Walker et al. 2022) |
| H425S | cac | agc | 2 | 14 | 0 | 2 | (Walker et al. 2022) |
| H445T | cac | acc | 1 | 121 |  | 7 | (Sandgren et al. 2009) |
| H445T | cac | acc | 1 | 871 | 0 | 6139 | (Zignol et al. 2018) |
| H425T | cac | acc | 3 | 3 | 0 | 0 | (Walker et al. 2022) |
| H445Y | cac | unkn. | 8 | 66 | 0 | 56 | (Telenti et al. 1993) |
| H445Y | cac | tac | 39 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| H445Y | cac | tac | 3 | 36 | 0 | 10 | (Bodmer et al. 1995) |
| H445Y | cac | tac | 1 | 163 |  |  | (Yang et al. 1998) |
| H445Y | cac | tac | 2 | 41 |  |  | (Cavusoglu et al. 2002) |
| H445Y | cac | tac | 9 | 109 | 0 |  | (Wang et al. 2007) |
| H445Y | cac | tac | 3 | 41 | 0 | 286 | (Bahrmand et al. 2009) |
| H445Y | cac | tac | 18 | 336 | 0 | 55 | (Rodwell et al. 2014) |
| H445Y | cac | tac | 2 | 36 | 0 | 5 | (Jamieson et al. 2014) |
| H445Y | cac | tac | 20 | 300 | 1 | 315 | (Van Deun et al. 2013) |
| H445Y | cac | tac | 3 | 84 | 0 | 36 | (Kambli et al. 2015) |
| H445Y | cac | tac | 1 | 49 | 0 | 114 | (Otchere et al. 2016) |
| H445Y | cac | tac | 3 | 57 | 0 |  | (ElMaraachli et al. 2015) |
| H445Y | cac | tac | 27 | 189 |  |  | (Rukasha et al. 2016) |
| H445Y | cac | tac | 2 |  | 0 |  | (Nosova et al. 2016) |
| H445Y | cac | tac | 1 | 102 | 0 | 62 | (Berrada et al. 2016) |
| H445Y | cac | tac | 2 | 256 | 0 |  | (Jing et al. 2017) |
| H445Y | cac | tac | 31 | 871 | 3 | 6139 | (Zignol et al. 2018) |
| H445Y | cac | unkn. | 1 | 139 | 0 | 17 | (Miotto et al. 2018) |
| H445Y | cac | unkn. | 4 | 52 |  |  | (Suthum, Samosornsuk, and Samosornsuk 2020) |
| H445Y | cac | tac | 4 | 154 |  |  | (Matsui et al. 2020) |
| H445Y | cac | tac | 6 | 324 | 0 | 28 | (Vargas et al. 2020) |
| H445Y | cac | tac | 305 | 347 | 2 | 4 | (Walker et al. 2022) |
| H445Y | cac | tac | 18 | 153 | 0 | 9 | (Campbell et al. 2011) |
| H445Y | cac | tac | 2 | 69 |  |  | (Madania et al. 2012) |
| K446E | aag | gag | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| K446Q | aag | cag | 1 | 108 | 0 | 12 | (Sandgren et al. 2009) |
| K446Q | aag | cag | 0 | 7 | 0 | 0 | (Walker et al. 2022) |
| K446N | aag | aat | 2 | 94 | 0 | 32 | (Sandgren et al. 2009) |
| K446R | aag | agg | 0 | 2 | 0 | 0 | (Walker et al. 2022) |
| K446T | aag | acg | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| R447H | cgc | cac | 2 | 94 | 0 | 32 | (Sandgren et al. 2009) |
| R447P | cgc | ccc | 4 | 94 | 0 | 32 | (Sandgren et al. 2009) |
| R447P | cgc | cct | 1 | 15 |  | 10 | (Sandgren et al. 2009) |
| R447R | cgc | cgt | 0 | 0 | 0 | 53 | (Walker et al. 2022) |
| R448Q | cga | caa | 2 | 6 | 0 | 0 | (Walker et al. 2022) |
| R448K | cga | unkn. | 1 | 871 | 0 | 6139 | (Zignol et al. 2018) |
| R448K | cga | aaa | 2 | 2 | 0 | 0 | (Walker et al. 2022) |
| R448R | cga | cgg | 0 | 0 | 0 | 1 | (Walker et al. 2022) |
| L449L | ctg | ctc | 0 | 2 | 0 | 0 | (Walker et al. 2022) |
| L449L | ctg | cta | 0 | 0 | 0 | 2 | (Walker et al. 2022) |
| L449M | ctg | atg | 0 | 9 | 0 | 0 | (Walker et al. 2022) |
| L449P | ctg | unkn. | 2 |  |  |  | (Singh et al. 2020) |
| S450C | tcg | gcg | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| S450C | tcg | tgt | 0 | 102 | 1 | 62 | (Berrada et al. 2016) |
| S450C | tcg | tgt | 1 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| S450C | tcg | unkn. | 1 | 871 | 1 | 6139 | (Zignol et al. 2018) |
| S450C | tcg | tgt | 0 | 0 | 1 | 1 | (Walker et al. 2022) |
| S450C | tcg | tgc | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| S450F | tcg | ttc | 1 | 102 | 0 | 62 | (Berrada et al. 2016) |
| S450F | tcg | ttt | 2 | 103 | 0 | 10 | (Sandgren et al. 2009) |
| S450F | tcg | unkn. | 2 | 139 | 0 | 17 | (Miotto et al. 2018) |
| S450F | tcg | ttc | 38 | 871 | 0 | 6139 | (Zignol et al. 2018) |
| S450F | tcg | ttc | 6 | 324 | 0 | 28 | (Vargas et al. 2020) |
| S450F | tcg | ttc | 70 | 77 | 0 | 0 | (Walker et al. 2022) |
| S450F | tcg | ttc | 1 | 153 | 0 | 9 | (Campbell et al. 2011) |
| S450F | tcg | ttt | 33 | 35 | 0 | 0 | (Walker et al. 2022) |
| S450G | tcg | ggg | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| S450G | tcg | ggg | 1 | 69 |  |  | (Madania et al. 2012) |
| S450L | tcg | unkn. | 31 | 66 | 0 | 56 | (Telenti et al. 1993) |
| S450L | tcg | ttg | 1 | 1 | 0 | 8 | (Sandgren et al. 2009) |
| S450L | tcg | ttg | 4 | 13 | 0 | 39 | (Heym et al. 1994) |
| S450L | tcg | ttg | 3 | 36 | 0 | 10 | (Bodmer et al. 1995) |
| S450L | tcg | ttg | 33 | 109 | 0 |  | (Wang et al. 2007) |
| S450L | tcg | ttg | 1 | 10 | 0 |  | (Zaczek et al. 2009) |
| S450L | tcg | ttg | 14 | 163 |  |  | (Yang et al. 1998) |
| S450L | tcg | ttg | 1 | 163 |  |  | (Yang et al. 1998) |
| S450L | tcg | ttg | 41 | 163 |  |  | (Yang et al. 1998) |
| S450L | tcg | ttg | 15 | 41 |  |  | (Cavusoglu et al. 2002) |
| S450L | tcg | ttg | 1 | 41 |  |  | (Cavusoglu et al. 2002) |
| S450L | tcg | ttg | 1 | 41 |  |  | (Cavusoglu et al. 2002) |
| S450L | tcg | ttg | 1 | 41 |  |  | (Cavusoglu et al. 2002) |
| S450L | tcg | ttg | 1 | 41 |  |  | (Cavusoglu et al. 2002) |
| S450L | tcg | ttg | 10 |  |  |  | (Springer et al. 2009) |
| S450L | tcg | ttg | 1 | 36 |  |  | (Sirgel et al. 2013) |
| S450L | tcg | ttg | 231 | 336 | 1 | 55 | (Rodwell et al. 2014) |
| S450L | tcg | unkn. | 170 | 300 | 9 | 315 | (Van Deun et al. 2013) |
| S450L | tcg | ttg | 13 |  |  |  | (Htike Min et al. 2014) |
| S450L | tcg | ttg | 19 | 36 | 0 | 5 | (Jamieson et al. 2014) |
| S450L | tcg | ttg | 14 | 57 | 0 |  | (ElMaraachli et al. 2015) |
| S450L | tcg | ttg | 26 | 49 | 0 | 114 | (Otchere et al. 2016) |
| S450L | tcg | ttg | 57 | 84 | 0 | 36 | (Kambli et al. 2015) |
| S450L | tcg | ttg | 93 |  | 0 |  | (Nosova et al. 2016) |
| S450L | tcg | ttg | 105 | 189 |  |  | (Rukasha et al. 2016) |
| S450L | tcg | ttg | 5 | 102 | 0 | 62 | (Berrada et al. 2016) |
| S450L | tcg | ttg | 156 | 256 | 0 |  | (Jing et al. 2017) |
| S450L | tcg | unkn. | 4 | 139 | 0 | 17 | (Miotto et al. 2018) |
| S450L | tcg | unkn. | 530 | 871 | 11 | 6139 | (Zignol et al. 2018) |
| S450L | tcg | ttg | 5 |  | 0 |  | (Torrea et al. 2019) |
| S450L | tcg | ttg | n.d. | 1302 | 3 |  | (Mvelase et al. 2019) |
| S450L | tcg | unkn. | 41 | 52 |  |  | (Suthum, Samosornsuk, and Samosornsuk 2020) |
| S450L | tcg | ttg | 107 | 154 |  |  | (Matsui et al. 2020) |
| S450L | tcg | ttg | 120 | 324 | 2 | 28 | (Vargas et al. 2020) |
| S450L | tcg | ttg | 5332 | 6536 | 67 | 74 | (Walker et al. 2022) |
| S450L | tcg | ttg | 101 | 153 | 0 | 9 | (Campbell et al. 2011) |
| S450L | tcg | ttg | 39 | 69 |  |  | (Madania et al. 2012) |
| S450L | tcg | ctg | 1 | 1 | 0 | 0 | (Walker et al. 2022) |
| S450M | tcg | atg | 1 | 324 | 2 | 28 | (Vargas et al. 2020) |
| S450M | tcg | atg | 5 | 5 | 0 | 0 | (Walker et al. 2022) |
| S450P | tcg | unkn. | n.d. | 1302 | 1 |  | (Mvelase et al. 2019) |
| S450Q | tcg | unkn. | 1 | 66 | 0 | 56 | (Telenti et al. 1993) |
| S450Q | tcg | cag | 1 | 121 | 0 | 7 | (Sandgren et al. 2009) |
| S450Q | tcg | cag | 1 | 189 |  |  | (Rukasha et al. 2016) |
| S450Q | tcg | cag | 1 | 256 | 0 |  | (Jing et al. 2017) |
| S450Q | tcg | unkn. | 1 | 139 | 0 | 17 | (Miotto et al. 2018) |
| S450Q | tcg | cag | 6 | 8 | 0 | 0 | (Walker et al. 2022) |
| S450V | tcg | gtg | 0 | 2 | 1 | 1 | (Walker et al. 2022) |
| S450W | tcg | unkn. | 1 | 66 | 0 | 56 | (Telenti et al. 1993) |
| S450W | tcg | tgg | 1 | 26 | 0 | 10 | (Bodmer et al. 1995) |
| S450W | tcg | tgg | 15 | 109 | 0 |  | (Wang et al. 2007) |
| S450W | tcg | tgg | 4 | 41 |  |  | (Cavusoglu et al. 2002) |
| S450W | tcg | unkn. | 3 | 300 | 0 | 315 | (Van Deun et al. 2013) |
| S450W | tcg | tgg | 7 | 336 | 0 | 55 | (Rodwell et al. 2014) |
| S450W | tcg | tgg | 3 | 36 | 0 | 5 | (Jamieson et al. 2014) |
| S450W | tcg | tgg | 5 | 57 | 0 |  | (ElMaraachli et al. 2015) |
| S450W | tcg | tgg | 1 |  | 0 |  | (Nosova et al. 2016) |
| S450W | tcg | tgg | 3 | 102 | 0 | 62 | (Berrada et al. 2016) |
| S450W | tcg | unkn. | 22 | 139 | 0 | 17 | (Miotto et al. 2018) |
| S450W | tcg | tgg | 9 | 871 | 0 | 6139 | (Zignol et al. 2018) |
| S450W | tcg | unkn. | 1 | 52 |  |  | (Suthum, Samosornsuk, and Samosornsuk 2020) |
| S450W | tcg | tgg | 8 | 154 |  |  | (Matsui et al. 2020) |
| S450W | tcg | tgg | 2 | 324 | 0 | 28 | (Vargas et al. 2020) |
| S450W | tcg | tgg | 127 | 151 | 5 | 5 | (Walker et al. 2022) |
| S450W | tcg | tgg | 2 | 153 | 0 | 9 | (Campbell et al. 2011) |
| S450W | tcg | tgg | 2 | 69 |  |  | (Madania et al. 2012) |
| S450Y | tcg | unkn. | 1 | 36 | 0 | 10 | (Bodmer et al. 1995) |
| S450Y | tcg | unkn. | 1 | 139 | 0 | 17 | (Miotto et al. 2018) |
| S450Y | tcg | tac | 2 | 2 | 0 | 0 | (Walker et al. 2022) |
| A451G | gcg | ggg | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| A451G | gcg | ggc | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| A451V | gcg | gtg | 0 | 7 | 4 | 4 | (Walker et al. 2022) |
| L452Q | ctg | cag | 0 | 0 | 1 | 1 | (Walker et al. 2022) |
| L452L | ctg | ttg | 0 | 0 | 0 | 1 | (Walker et al. 2022) |
| L452L | ctg | ctt | 0 | 1 | 0 | 1 | (Walker et al. 2022) |
| L452M | ctg | atg | 0 | 0 | 1 | 1 | (Walker et al. 2022) |
| L452P | ctg | unkn. | 1 | 66 | 0 | 56 | (Telenti et al. 1993) |
| L452P | ctg | ccg | 1 | 24 | 0 | 0 | (Sandgren et al. 2009) |
| L452P | ctg | ccg |  |  |  |  | (Yang et al. 1998) |
| L452P | ctg | ccg | 0 | 41 | 1 |  | (Cavusoglu et al. 2002) |
| L452P | ctg | ccg | 0 | 41 | 1 |  | (Cavusoglu et al. 2002) |
| L452P | ctg | unkn. | 9 | 300 | 1 | 315 | (Van Deun et al. 2013) |
| L452P | ctg | ccg |  |  |  |  | (Somoskovi et al. 2013) |
| L452P | ctg | ccg | 4 | 84 | 0 | 36 | (Kambli et al. 2015)  |
| L452P | ctg | ccg | 0 | 102 | 2 | 62 | (Berrada et al. 2016) |
| L452P | ctg | ccg | 3 | 256 | 0 |  | (Jing et al. 2017) |
| L452P | ctg | unkn. | 11 | 139 | 2 | 17 | (Miotto et al. 2018) |
| L452P | ctg | unkn. | 12 | 871 | 15 | 6139 | (Zignol et al. 2018) |
| L452P | ctg | ccg | 6 |  | 3 |  | (Torrea et al. 2019) |
| L452P | ctg | unkn. | 1 | 14 |  |  | (Solari, Santos-Lazaro, and Puyen 2020) |
| L452P | ctg | unkn. | 1 | 52 |  |  | (Suthum, Samosornsuk, and Samosornsuk 2020) |
| L452P | ctg | ccg | 1 | 154 |  |  | (Matsui et al. 2020) |
| L452P | ctg | unkn. | 0 | 324 | 4 | 28 | (Vargas et al. 2020) |
| L452P | ctg | ccg | 78 | 121 | 50 | 53 | (Walker et al. 2022) |
| L452P | ctg | ccg | 1 | 153 | 2 | 9 | (Campbell et al. 2011) |
| L452P | ctg | ccg | 3 | 69 |  |  | (Madania et al. 2012) |
| L452P | ctg | cct | 2 | 82 | 0 | 18 | (Sandgren et al. 2009) |
| L452P | ctg | ccc | 4 | 189 |  |  | (Rukasha et al. 2016) |
| L452V | ctg | gtg | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| P454H | ccc | cac | 1 | 154 | 0 | 113 | (Sandgren et al. 2009) |
| P454H | ccc | cac | 0 | 2 | 2 | 2 | (Walker et al. 2022) |
| P454L | ccc | ctc | 0 | 0 | 6 | 6 | (Walker et al. 2022) |
| P454R | ccc | cgc | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| P454S |   | unkn. | 0 | 300 | 3 | 315 | (Van Deun et al. 2013) |
| P454S | ccc | tcc | 4 | 51 | 0 | 19 | (Sandgren et al. 2009) |
| P454S | ccc | tcc | 0 | 1 | 1 | 1 | (Walker et al. 2022) |
| G455G | ggc | ggg | 4 |  |  |  | (Htike Min et al. 2014) |
| G455G | ggc | ggt | 0 | 0 | 0 | 2 | (Walker et al. 2022) |
| L457R | ctg | cgt | 1 |  |  |  | (Htike Min et al. 2014) |
| L457P | ctg | ccg | 1 | 112 | 0 | 30 | (Sandgren et al. 2009) |
| E460G | gag | ggg | 1 | 154 | 0 | 113 | (Sandgren et al. 2009) |
| E460G | gag | gat | 1 | 37 |  |  | (Sandgren et al. 2009) |
| E460G | gag | ggg | 0 | 5 | 0 | 2 | (Walker et al. 2022) |
| L464L | ctg | ttg | 0 | 0 | 0 | 1 | (Walker et al. 2022) |
| L464M | ctc  | atg | 3 | 19 | 0 | 22 | (Sandgren et al. 2009) |
| S472A | tcg | gcg | 1 | 37 | 0 | 0 | (Sandgren et al. 2009) |
| I480I | atc | att | 0 | 0 | 0 | 1 | (Walker et al. 2022) |
| I480T | atc | acc | 1 | 111 | 0 | 0 | (Sandgren et al. 2009) |
| I480T | atc | acc | 0 | 3 | 0 | 0 | (Walker et al. 2022) |
| I480V | atc | gtc | 1 | 37 | 0 | 13 | (Sandgren et al. 2009) |
| I480V | atc | gtc | 0 | 43 | 0 | 2 | (Walker et al. 2022) |
| E481A | gaa | gca | 0 | 8 | 0 | 0 | (Walker et al. 2022) |
| E481E | gaa | gag | 0 | 0 | 0 | 1 | (Walker et al. 2022) |
| E481G | gaa | gga | 1 | 122 |  |  | (Sandgren et al. 2009) |
| P483S | cct | tct | 0 | 2 | 0 | 0 | (Walker et al. 2022) |
| P483L | cct | ctt | 1 | 122 |  |  | (Sandgren et al. 2009) |
| P483L | cct | ctt | 0 | 2 | 1 | 1 | (Walker et al. 2022) |
| N487H | acc | cac | 0 | 2 | 0 | 0 | (Walker et al. 2022) |
| N487S | acc | agc | 0 | 3 | 0 | 1 | (Walker et al. 2022) |
| N487N | acc | aat | 0 | 4 | 0 | 1 | (Walker et al. 2022) |
| L490L | ctg | ttg | 0 | 0 | 0 | 1 | (Walker et al. 2022) |
| L490L | ctg | ctt | 0 | 0 | 0 | 3 | (Walker et al. 2022) |
| L490V | ctg | gtg | 2 | 111 |  |  | (Sandgren et al. 2009) |
| L490V | ctg | gtg | 0 | 2 | 0 | 0 | (Walker et al. 2022) |
| I491F | atc | unkn. | 5 | 300 | 0 | 315 | (Van Deun et al. 2013) |
| I491F | atc | ttc | 1 | 33 |  | 17 | (Sandgren et al. 2009) |
| I491F | atc | ttc | 3 | 256 | 0 |  | (Jing et al. 2017) |
| I491F | atc | unkn. | 3 | 871 | 2 | 6139 | (Zignol et al. 2018) |
| I491F | atc | unkn. | 6 |  | 2 |  | (Torrea et al. 2019) |
| I491F | atc | unkn. | 2 |  |  |  | (Solari, Santos-Lazaro, and Puyen 2020) |
| I491F | atc | ttc | 1 | 324 | 2 | 28 | (Vargas et al. 2020) |
| I491F | atc | unkn. |  |  |  |  | (Ardizzoni et al. 2021)  |
| I491F | atc | ttc | 45 | 54 | 53 | 57 | (Walker et al. 2022) |
| I491F | atc | ttc | 1 | 69 |  |  | (Madania et al. 2012) |
| I491L | atc | ctc | 0 | 25 | 0 | 0 | (Walker et al. 2022) |
| I491M | atc | atg | 2 | 14 | 2 | 3 | (Walker et al. 2022) |
| I491S | atc | agc | 0 | 1 | 0 | 0 | (Walker et al. 2022) |
| I491T | atc | acc | 0 | 6 | 0 | 0 | (Walker et al. 2022) |
| I491V | atc | gtc | 0 | 8 | 0 | 0 | (Walker et al. 2022) |
| I491Y | atc | tac | 1 | 154 |  |  | (Matsui et al. 2020) |
| I491Y | atc | tac | 3 | 3 | 0 | 0 | (Walker et al. 2022) |
| S493L | tcg | ttg | 1 | 221 | 0 | 29 | (Sandgren et al. 2009) |
| S493L | tcg | ttg | 0 | 5 | 0 | 1 | (Walker et al. 2022) |
| S493W | tcg | tgg | 0 | 0 | 3 | 3 | (Walker et al. 2022) |
| L494L | ctg | cta | 0 | 1 | 0 | 11 | (Walker et al. 2022) |
| S541A | tcg | gcg | 1 | 154 | 0 | 113 | (Sandgren et al. 2009) |
| R552C | cgc | tgc | 1 | 111 |  |  | (Sandgren et al. 2009) |
| G591D | gag | gat | 1 | 111 |  |  | (Sandgren et al. 2009) |
| A692T | gcc | acc | 1 | 324 | 0 | 28 | (Vargas et al. 2020) |
| V695L | gtg | unkn. | 1 | 14 |  |  | (Solari, Santos-Lazaro, and Puyen 2020) |
| V695L | gtg | ctg | 1 | 324 | 4 | 28 | (Vargas et al. 2020) |
| R741S | cac | tgt | 1 | 324 | 0 | 28 | (Vargas et al. 2020) |
| I965V | unkn. | unkn. | 0 | 324 | 3 | 28 | (Vargas et al. 2020) |
| Q980R | unkn. | unkn. | 1 | 324 | 0 | 28 | (Vargas et al. 2020) |
| R1163H | cgc | cac | 0 | 324 | 1 | 28 | (Vargas et al. 2020) |

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## Table S2.

Statistically significant list of genes based on dN/dS, d2N/d1N, and d2N/dS ratios statistics. Association of measures with drug resistance (a), gene-gene pairwise comparisons for source mutation frequencies (b), gene-gene pairwise comparisons for phylogenetically-adjusted frequencies (c), and individual codon mutation frequencies deviations from the expected values (d) approaches were used.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Gene | Resistance, or resistance-associated gene\* | Number of S mutations | Number of 1N mutations | Number of 2N mutations | Odds ratio | -*log*(*p*-value) \* |
| dN/dS | d2N/d1N | d2N/dS | dN/dS | d2N/d1N | d2N/dS |
| *pncA* | R | 25 | 886 | 0 | 17.40 | 0.00 | 0.00 | **71.30** | **4.30** |  |
| *rpoB* | R | 108 | 2108 | 43 | 10.44 | 3.76 | 38.67 | **151.73** |  | **28.16** |
| *cut1* | R | 9 | 160 | 0 | 9.29 | 0.00 | 0.00 | **11.07** | **8.67** |  |
| *pstP* |  | 89 | 1705 | 0 | 8.67 | 0.00 | 0.00 | **99.79** | **6.81** |  |
| *dipZ* |  | 83 | 2599 | 1 | 7.78 | 0.01 | 0.12 | **90.17** | **17.27** |  |
| *cyp138* |  | 64 | 108 | 350 | 6.68 | 19.20 | 35.34 | **37.43** | **62.27** | **84.25** |
| *katG* | R | 100 | 1396 | 23 | 5.79 | 2.21 | 12.65 | **61.19** |  | **9.87** |
| *Rv0988* |  | 211 | 271 | 244 | 1.81 | 10.14 | 10.51 | **6.99** | **41.54** | **40.39** |
| *Rv2082* |  | 819 | 1223 | 0 | 1.25 | 0.00 | 0.00 | 3.40 | **8.45** | **6.86** |
| *Rv2024c* |  | 102 | 189 | 42 | 0.94 | 52.00 | 40.35 | 0.10 | **12.30** | **9.23** |
| *recC* |  | 807 | 183 | 1 | 0.13 | 0.08 | 0.01 | **92.24** |  | **17.63** |
| *Rv1190* |  | 347 | 50 | 0 | 0.10 | 0.00 | 0.00 | **42.76** |  | **5.30** |
| *mce1F* |  | 2201 | 205 | 1 | 0.06 | 0.23 | 0.01 | **200.00** |  | **14.88** |
| *Rv1977* |   | 684 | 68 | 0 | 0.05 | 0.00 | 0.00 | **128.47** |   | **5.68** |
| *hsaB* |  | 24 | 1553 | 0 | 36.73 | 0.00 | 0.00 | **161.74** |  |  |
| *Rv0192* |  | 42 | 1520 | 1 | 20.45 | 0.11 | 2.24 | **140.61** |  |  |
| *cobD* |  | 50 | 2043 | 0 | 12.76 | 0.00 | 0.00 | **105.15** |  |  |
| *murD* |  | 55 | 1171 | 1 | 12.13 | 0.13 | 1.62 | **93.14** |  |  |
| *Rv0395* |  | 16 | 326 | 0 | 12.04 |  |  | **26.84** |  |  |
| *rpsL* | R | 26 | 572 | 2 | 8.73 | 0.37 | 3.27 | **30.87** |  |  |
| *Rv0315* |  | 29 | 361 | 0 | 7.95 | 0.00 | 0.00 | **26.09** | 0.80 | 0.00 |
| *Rv2668* |  | 12 | 222 | 0 | 7.90 |  |  | **12.26** | 0.00 | 0.00 |
| *rbsK* |  | 28 | 371 | 0 | 7.32 | 0.00 | 0.00 | **23.32** |  |  |
| *Rv1760* |  | 33 | 521 | 0 | 7.29 | 0.00 | 0.00 | **28.69** |  |  |
| *proB* |  | 53 | 871 | 0 | 7.07 | 0.00 | 0.00 | **44.49** |  |  |
| *Rv0538* |  | 58 | 680 | 0 | 6.92 | 0.00 | 0.00 | **42.86** |  |  |
| *Rv0064* |  | 149 | 1842 | 1 | 6.24 | 0.10 | 0.64 | **97.02** |  |  |
| *Rv0318c* |  | 31 | 342 | 1 | 6.11 | 0.10 | 0.61 | **19.39** | 2.00 | 0.00 |
| *Rv3657c* |  | 17 | 105 | 0 | 5.98 |  |  | **8.45** | 0.00 | 0.00 |
| *Rv0398c* |  | 23 | 437 | 0 | 5.69 |  |  | **15.08** | 0.00 | 0.00 |
| *bioD* |  | 27 | 241 | 0 | 5.06 |  |  | **12.31** | 0.00 | 0.00 |
| *ponA1* |  | 88 | 811 | 0 | 5.02 | 0.00 | 0.00 | **38.92** |  |  |
| *Rv1230c* |  | 39 | 253 | 1 | 4.91 | 0.66 | 3.23 | **15.07** | 0.00 | 0.37 |
| *gid* | R | 79 | 682 | 7 | 4.54 | 0.64 | 2.91 | **29.68** |  |  |
| *phoR* |  | 49 | 376 | 1 | 4.27 | 0.24 | 1.03 | **16.28** | 0.50 | 0.00 |
| *murG* |  | 53 | 367 | 0 | 4.09 | 0.00 | 0.00 | **15.90** |  |  |
| *Rv0218* |  | 42 | 424 | 0 | 3.96 | 0.00 | 0.00 | **13.62** | 0.71 | 0.00 |
| *ddlA* |  | 37 | 194 | 0 | 3.86 |  |  | **9.30** | 0.00 | 0.00 |
| *ethA* | R | 64 | 447 | 3 | 3.44 | 0.32 | 1.13 | **14.40** | 0.95 | 0.00 |
| *Rv1129c* | R | 39 | 212 | 0 | 3.42 | 0.00 | 0.00 | **8.15** | 0.75 | 0.00 |
| *gyrA* | R | 194 | 1308 | 2 | 3.34 | 0.19 | 0.64 | **39.66** |  |  |
| *whiB6* | R | 33 | 230 | 1 | 3.27 | 0.26 | 0.85 | **6.95** | 0.49 | 0.00 |
| *Rv2264c* |  | 75 | 423 | 0 | 3.14 | 0.00 | 0.00 | **13.22** | 0.37 | 0.00 |
| *rpoC* | R | 136 | 786 | 3 | 3.04 | 0.29 | 0.88 | **22.32** |  |  |
| *cycA* |  | 80 | 239 | 0 | 2.72 | 0.00 | 0.00 | **8.38** | 0.77 | 0.26 |
| *embB* | R | 154 | 1485 | 0 | 2.70 | 0.00 | 0.00 | **22.48** | 1.00 | 0.25 |
| *Rv1461* |  | 80 | 349 | 0 | 2.47 | 0.00 | 0.00 | **7.92** | 0.36 | 0.00 |
| *Rv3433c* |  | 993 | 1010 | 0 | 0.65 | 0.00 | 0.00 | **10.45** | 1.74 | 2.48 |
| *aftD* |  | 916 | 825 | 1 | 0.56 | 0.11 | 0.06 | **16.04** | 2.03 | 3.56 |
| *ppsD* |  | 261 | 217 | 0 | 0.47 | 0.00 | 0.00 | **7.84** | 0.29 | 0.79 |
| *mmpL4* |  | 151 | 125 | 0 | 0.37 | 0.00 | 0.00 | **7.50** | 0.00 | 0.44 |
| *recD* |  | 196 | 107 | 0 | 0.35 | 0.00 | 0.00 | **9.51** | 0.27 | 0.84 |
| *dctA* |  | 342 | 83 | 0 | 0.33 | 0.00 | 0.00 | **11.96** | 0.00 | 0.38 |
| *serA1* |  | 120 | 73 | 0 | 0.29 | 0.00 | 0.00 | **8.05** | 0.79 | 2.25 |
| *hemE* |  | 145 | 41 | 0 | 0.29 |  |  | **7.32** | 0.00 | 0.00 |
| *Rv2081c* |  | 91 | 54 | 2 | 0.27 | 1.85 | 0.49 | **6.95** | 0.21 | 0.22 |
| *eccC5* |  | 193 | 93 | 0 | 0.26 | 0.00 | 0.00 | **13.79** | 0.26 | 0.92 |
| *Rv1501* |  | 149 | 74 | 0 | 0.25 |  |  | **11.82** | 0.00 | 0.00 |
| *Rv2319c* |  | 160 | 56 | 1 | 0.22 | 0.78 | 0.17 | **12.97** | 0.00 | 0.91 |
| *Rv3528c* |  | 374 | 92 | 0 | 0.18 | 0.00 | 0.00 | **33.61** |  |  |
| *Rv0575c* |  | 218 | 81 | 1 | 0.17 | 1.27 | 0.21 | **24.08** | 0.00 | 0.66 |
| *Rv0376c* |  | 2498 | 336 | 1 | 0.17 | 1.25 | 0.21 | **170.00** |  |  |
| *Rv0986* |  | 218 | 60 | 1 | 0.17 | 2.90 | 0.48 | **22.13** | 0.35 | 0.26 |
| *ruvB* |  | 176 | 41 | 0 | 0.14 | 0.00 | 0.00 | **19.36** | 0.00 | 0.98 |
| *Rv2052c* |  | 852 | 131 | 0 | 0.10 | 0.00 | 0.00 | **113.93** |  |  |
| *Rv3228* | R | 521 | 75 | 0 | 0.09 | 0.00 | 0.00 | **68.81** |  |  |
| *Rv1319c* |  | 162 | 23 | 7 | 0.06 | 21.46 | 1.06 | **31.84** |  |  |
| *Rv1762c* |  | 144 | 26 | 0 | 0.04 | 0.00 | 0.00 | **34.81** |  |  |
| *relG* |  | 1339 | 12 | 0 | 0.01 | 0.00 | 0.00 | **181.38** |  |  |
| *Rv1573* |   | 667 | 8 | 0 | 0.01 | 0.00 | 0.00 | **142.67** |   |   |

## Table S3.

Statistically significant list of genes of *Neisseria gonorrhoeae* based on dN/dS, d2N/d1N, and d2N/dS ratios statistics.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Gene | Number of S mutations | Number of 1N mutations | Number of 2N mutations | Odds ratio | -*log*(*p*-value) \* |
| dN/dS | d2N/d1N | d2N/dS | dN/dS | d2N/d1N | d2N/dS |
| NGK\_RS00205 | 363 | 88 | 23 | 4.4 | 14.9 | 62.2 | **24.3** | 3.8 | **11.0** |
| NGK\_RS06565 | 638 | 78 | 24 | 7.1 | 5.0 | 34.7 | **52.8** | 2.4 | **13.1** |
| NGK\_RS06660 | 538 | 135 | 18 | 3.7 | 6.0 | 21.9 | **28.0** | 2.3 | **7.3** |
| NGK\_RS06730 | 2255 | 381 | 35 | 3.9 | 6.3 | 24.2 | **97.2** | **4.6** | **15.3** |
| NGK\_RS08025 | 2766 | 295 | 28 | 6.4 | 1.9 | 11.8 | **180.9** | 1.0 | **11.9** |
| NGK\_RS08860 | 1133 | 288 | 20 | 4.1 | 1.8 | 7.3 | **67.9** | 0.6 | **5.8** |
| NGK\_RS09060 | 886 | 324 | 23 | 2.7 | 5.4 | 14.4 | **31.9** | 2.7 | **7.5** |
| NGK\_RS09405 | 329 | 50 | 24 | 10.2 | 11.9 | 114.2 | **45.3** | 2.9 | **15.1** |
| NGK\_RS09735 | 2564 | 178 | 13 | 8.9 | 1.2 | 11.0 | **189.5** | 0.1 | **6.3** |
| NGK\_RS09870 | 1874 | 266 | 11 | 4.7 | 2.5 | 11.8 | **95.9** | 0.8 | **4.6** |
| NGK\_RS11680 | 613 | 169 | 23 | 4.2 | 7.1 | 28.9 | **39.8** | 2.9 | **9.9** |
| NGK\_RS14155 | 117 | 25 | 12 | 5.9 | 7.3 | 39.4 | **11.1** | 1.5 | **5.7** |
| NGK\_RS15570 | 2110 | 206 | 27 | 6.3 | 1.9 | 11.6 | **128.5** | 0.9 | **11.4** |
| NGK\_RS15575 | 2001 | 116 | 29 | 10.0 | 2.8 | 27.8 | **148.5** | 2.0 | **18.0** |
| NGK\_RS15580 | 1692 | 127 | 10 | 8.8 | 1.6 | 14.3 | **129.2** | 0.2 | **5.4** |
|  |  |  |  |  |  |  |  |  |  |