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Characterization of genomic variations in SNPs of PE_PGRS genes reveals deletions and insertions in extensively drug resistant (XDR) M. tuberculosis strains from Pakistan.

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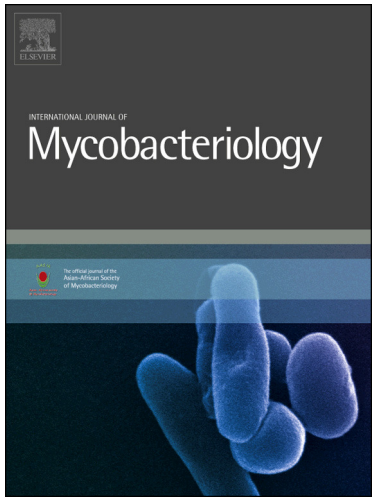

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Characterization of genomic variations in SNPs of PE_PGRS genes reveals deletions and insertions in extensively drug resistant (XDR) *M. tuberculosis* strains from Pakistan

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Running Title: Genomic variations in SNPs of PE_PGRS genes in XDR MTB strains

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ABSTRACT

Background: *Mycobacterium tuberculosis* (MTB) PE_PGRS genes belong to the PE multigene family. Although the function of PE-PGRS genes is unknown, it is hypothesized that the PE_PGRS genes may be associated with antigenic variability in MTB.

Material and methods: Whole Genome Sequencing analysis was performed on (n=37) extensively drug-resistant (XDR) MTB strains from Pakistan, which included Lineage 1 (East African Indian, n=2); Other lineage 1 (n=3); Lineage 3 (Central Asian, n=24); Other lineage 3 (n=4); Lineage 4 (X3, n=1) and T group (n=3) MTB strains.

Results: There were 107 SNPs identified from the analysis of 42 PE_PGRS genes; of these, 13 were non-synonymous SNPs (nsSNPs). The nsSNPs identified in PE_PGRS genes–6, 9 and 10–were common in all EAI, CAS, Other lineages (1 and 3), T1 and X3. Deletions (DELs) in PE_PGRS genes–3 and 19–were observed in 17 (80.9%) CAS1 and 6 (85.7%) in Other lineage (1 and 3) XDR MTB strains, while DELs in the PE_PGRS49 were observed in all CAS1, CAS, CAS2 and Other lineage (1 and 3) XDR MTB strains. All CAS, EAI and Other lineage (1 and 3) strains showed insertions (INS) in PE_PGRS6 gene, while INS in the PE_PGRS genes 19 and 33 were observed in 20 (95.2%) CAS1, all CAS, CAS2, EAI and Other lineage (1 and 3) XDR MTB strains.

Conclusion: Genetic diversity in PE_PGRS genes contributes to antigenic variability and may result in increased immunogenicity of strains. This is the first study identifying variations in nsSNPs and INDELs in the PE_PGRS genes of XDR-TB strains from Pakistan. It highlights common genetic variations which may contribute to persistence.

1. Introduction

Mycobacterium tuberculosis (MTB), the causative agents of tuberculosis (TB) kills approximately 2 million people worldwide each year [1]. The control of TB requires a better understanding of the mechanisms that allow MTB to evade the immune system and remain persistent with the host. The sequencing of the genomes of MTB strains has provided important insights into possible mechanisms of persistence within the host, along with the discovery of ~60 genes named PE_PGRS (Proline glutamic acid polymorphic GC rich repetitive sequence), which belong to the PE multigene family [2]. These multigene families represent approximately 10% of the coding capacity of the MTB genome and are characterized by their high GC content and repetitive sequences. This may be due to the high frequency of gene duplication, recombination and strand slippage mechanisms [2, 3].

The single nucleotide polymorphisms (SNPs) have been shown to be the most common form of genetic variation in MTB complex (MTBC). The SNPs have been shown to be of low frequency and limited horizontal gene transfer (HGT), which have resulted in low levels of independent occurrence of the same SNP in phylogenetically unrelated strains [4, 5]. Depending on their position in the genome, SNPs can be either coding or non-coding. The coding density in the MTBC has been reported to be 90%-96%, with most of the SNPs in the MTBC in the coding region of the genome [6]. SNPs which results in an amino acid change are non-synonymous (nsSNPs) while those which do not cause a change in amino acid coding are synonymous (sSNPs).

While the function of the members of the PE_PGRS multigene family is not known, it is hypothesized that the PE_PGRS genes may be associated with antigenic and genetic variability

as well as virulence [7-10]. Previous studies have been shown that some members of the PE_PGRS family are expressed on the cell surface during MTB infection and recognized by the host immune system [7, 11, 12]. It has been suggested that MTB PE_PGRS genes are variably expressed during infection [13-15]. The roles of PE_PGRS16 and PE_PGRS26 in causing infection have previously been studied in mouse models; the expression of PE_PGRS16 was significantly up-regulated as compared with PE_PGRS26, suggesting that these two PE_PGRS genes may serve as a marker of latent TB infection [14]. In addition, PE_PGRS33 gene has been shown to encode for a surface expressed protein, while transposon mutagenesis-based studies have shown that the MTB PE_PGRS33 gene plays an important role in interactions with other mycobacteria as well as with macrophages [16].

The sequence variations such as SNPs, insertions and deletions (INDELs) in MTB clinical strains have also been investigated for PE_PGRS16, PE_PGRS26 and PE_PGRS33 [17, 18]. Moreover, in a population-based study of 649 clinical MTB strains, patients infected with MTB strains with a significant change in the PE_PGRS33 protein were more likely to belong to a cluster of TB cases as compared with MTB strains with minimal changes to the PE_PGRS33 protein suggests that PE_PGRS33 may play an important role in MTB transmission [19].

The extensively drug-resistant tuberculosis (XDR-TB) has emerged worldwide as one of the biggest threats to public health and TB control programs. XDR-TB is defined as TB caused by the MTB strain that is resistant to at least rifampin (RIF) and isoniazid (INH) among the first-line anti-TB drugs and resistant to fluoroquinolones and to at least one of the three injectable second-line drugs [20-22].

Previous studies have reported SNPs in MTBC as drug resistance-conferring mutations, with 1,447 mutations significant for most anti-TB drugs [23-26]. However, no data are available on sequence variations such as SNPs and INDELs in the PE_PGRS genes of XDR MTB isolates. This study analyzed 37 XDR MTB strains for the presence of SNPs, INDELs by whole genome sequencing (WGS) analysis method. The aim of this study is to specifically investigate SNPs and INDELs in XDR MTB strains to understand how genetic diversity contributes to antigenic variability.

2. Methodology

2.1 Strain selection

The MTB strains were obtained from the strain bank of Aga Khan University Clinical Microbiology Laboratory, Pakistan. The 37 XDR MTB strains were from the period of 2004-2009, which had previously been spoligotyped [27-29], and were randomly selected for the WGS analysis. The study samples selected for the WGS analysis belonged to all three Principal Genetic Groups: PGG1, PGG2 and PGG3, which were comprised of PGG1: 21 CAS1, 2 CAS, 1 CAS2, 2 EAI and 7 Other lineages (1 and 3) (89.2%); PGG2: 1 X3 (2.7%); and PGG3: 3 T (8.1%) groups, respectively.

2.2 Culture and antibiotic susceptibility testing

The XDR MTB strains used had been isolated from the specimens using Lowenstein-Jensen media and MGIT (Becton Dickinson, Franklin Lakes, NJ, and USA). MTB was identified using BACTEC NAP TB differentiation test (Becton Dickinson), growth on para-nitrobenzoic acid

containing media, nitrate reduction, and niacin accumulation [30, 31]. The drug susceptibility testing (DST) of these isolates was previously performed using an agar proportion method on enriched Middlebrook 7H10 medium (BBL Microbiology Systems, Cockeysville, MD, USA) at the following concentrations: rifampicin 1 µg/mL, isoniazid 0.2 µg/mL, streptomycin 2 µg/mL and 10 µg/mL, and ethambutol 5 µg/mL. Pyrazinamide sensitivity was determined by using BACTEC 7H12 medium, pH 6.0, at 100 µg/mL (BACTEC PZA test medium, Becton Dickinson). MDR TB strains were further tested with capreomycin 10 µg/mL, ciprofloxacin 2 µg/mL, ethionamide 5 µg/mL, amikacin 5µg/mL, and kanamycin 6µg/mL. Reference strain MTB H37Rv was used as a control with each susceptibility testing batch [32].

2.3 DNA extraction and spoligotyping

Spoligotyping was performed as described previously [33] and inferred *in silico*; the spoligotypes were also confirmed from the sequencing reads using SpolPred software [34].

2.4 Whole genome sequencing of MTB strains

DNA was extracted by the Cetyl-trimethyl ammonium bromide (CTAB) method [35]. All samples (n=37) underwent WGS with 76-base paired end fragment sizes using Illumina paired end HiSeq2000 technology. Briefly, the raw sequence data were mapped distinctively to the H37Rv reference genome. The resulting alignments allowed SNPs and small INDELs to be called using SAMtools/BCFtools (http://samtools.sourceforge.net), as well as larger INDELs using a consensus from paired end mapping distance or split read approaches 21-24.

Only those variants of high quality (at least Q30, equating to 1 error per 1000) and supported by bi-directional reads were retained. Spoligotypes were inferred from the sequencing reads SpolPred software [34]. The raw data files were analyzed using R to determine the presence of PE_PGRS INDELs in genomes of 37 XDR MTB strains.

3. Results

3.1 Detection of number of copies of PE_PGRS genes in the XDR MTB strains

Forty-two PE_PGRS genes were analyzed in 37 XDR MTB strains. The numbers of copies of PE_PGRS genes were variable and show no significant differences amongst the CAS1, CAS, CAS2, EAI, Other (lineages 1 and 3), T and X3 XDR MTB strains ($P>0.05$) analyzed by Pearson's Chi-square test **(Table 1)**.

3.2 Detection of SNPs in PE_PGRS genes of XDR **MTB** *strains*

A total of 107 SNPs were observed, including 13 nsSNPs in 37 XDR MTB strains. All CAS1, CAS, CAS2, EAI, Other (lineages 1 and 3) and X3 XDR MTB strains showed nsSNPs in the PGRS genes 6, 7, 9 and 10. Whereas 20 (95%) CAS1 XDR MTB strains showed nsSNPs in PE_PGRS17 and PE_PGRS37; 18 (85.7%) in PE_PGRS55 genes. However, all CAS, CAS2, EAI, Other (lineages 1 and 3), T1 and X3 XDR MTB strains showed nsSNPs in PE_PGRS17 and 37 genes. Additionally, all CAS2, EAI, T1 and X3 XDR MTB strains revealed nsSNPs in the PE_PGRS47 gene **(Table 2).**

3.3 Detection of deletions in the PE_PGRS genes of XDR **MTB** *strains*

Thirty-nine PE_PGRS genes (92.8%) were observed to have variable DELs in the CAS1, CAS, CAS2, EAI, Orphan, T1 and X3 XDR MTB strains. However, all CAS1, CAS, CAS2 and Other (lineages 1 and 3) XDR MTB strains were observed to have 1-36bp DEL in PE_ PGRS49, while all CAS, CAS2 and Other (lineages 1 and 3) XDR MTB strains showed 1-18bp DEL in PE_PGRS50 gene sequences. The 6-36 bps DEL in the PE_PGRS19 gene was observed in 17

(81.0%) CAS1, 6 (85.7%) Other lineage (1 and 3), all CAS, CAS2 and EAI XDR MTB strains. The DELs in the PE_PGRS5 and PE_PGRS49 genes were significantly more (p=0.0002, p=0.0216) in XDR CAS1 compared with XDR other lineages (T1 and X3), respectively, analyzed by Pearson's Chi-square test **(Table 3)**.

3.4 Detection of insertions in the PE_PGRS genes of XDR MTB strains

Thirty-nine PE_PGRS genes (92.8%) were observed to have variable INS in the CAS1. CAS, CAS2, EAI, Other lineage (1 and 3), T1 and X3 XDR MTB strains. The INS in the PE_PGRS51 gene was present in 35 (94.6%) with a 9bp INS, while PE_PGRS53 INS was present in 36 (97.3%) of XDR MTB strains with INS size range of 9-18bps. The INS in the PE_PGRS genes 6, 19, 28, 30, 33, 50, 57 and 61 were variably present in the XDR MTB strains with INS size ranging from 1-21bps.

The INS were also observed to be significantly more in PE_PGRS6 (p=0.05) and PE_PGRS30 (p=0.0447) in XDR CAS1 as compared with XDR other lineages strains (T1 and X3) groups analyzed by Pearson's Chi-square test **(Table 4)**.

3.5 Genetic diversity amongst the XDR MTB Principal Genetic Groups (PGG)

Of the 42 PE_PGRS genes investigated for detection of 37 XDR MTB strains by WGS, 34 (91.90%), 1 (2.7%) and 3 (8.1%) of the 37 MTB strains belonged to PGG1, PGG2 and PGG3, respectively. CAS1, CAS CAS2, EAI and Orphan belong to PGG1, while X3 and T1 belong to the PGG2 and PGG3 groups, respectively. There were significantly more nsSNPs present in

PGG1 strains (n=34) as compared with PGG2 (n=1) and PGG3 (n=2) strains **(Figure 1)**. However, given the larger proportion of PGG1 strains in this sample size of XDR strains as compared with others, it is difficult to get a complete picture for this comparison.

4. Discussion

The PE_PGRS genes have been shown to be limited to mycobacterial species; they have specially expanded within the genomes of pathogenic mycobacteria, probably through widespread gene duplication events and genetic divergence during their adaptation to the intra-macrophage environment [9].

It has been hypothesized that gene conversion may have contributed to the evolution of members of the PE_PGRS subfamily and may have participated in the generation of antigenic variation in their members [2, 7, 17]. A previous study has shown nucleotide substitution of A to G in the PE_PGRS17 genes of CAS, EAI and LAM strains. In addition, SNPs of G to A, C to A and G to C nucleotide substitutions were observed in PE_PGRS18 genes of CAS, EAI, LAM and Haarlem MTB strains [36].

The PGG1 is considered to be the most ancient of the MTB lineages, which has also been reported for other regions of Asia [37]. In this study, it was observed that all XDR MTB strains belonging to the PGG1 group had nsSNPs in the PE_PGRS6, 7, 9, 10, 13 and 32 genes, whereas it was variable in the PGG2 and PGG3 XDR MTB strains. However, the large proportion of PGG1 strains in this study as compared with PGG2 and PGG3 strains makes it difficult to get a complete picture of the proportion of SNPs. In this study, the nucleotide substitution of A to G and T to C in the PE_PGRS17 genes of CAS1, CAS, CAS2, EAI, T, X and orphan (lineages 1

and 3) XDR MTB strains was also observed. Moreover, nucleotide substitution of A to G, C to T and A to C in the PE_PGRS18 genes of CAS1, CAS, CAS2, EAI3, T, X and Other lineages (1 and 3) XDR MTB strains was also observed. However, the function of these PE_PGRS genes are yet unknown [36].

In a population-based study of 649 MTB clinical isolates it was shown that in PE_PGRS33 gene, Thr47Ile was found in 1 isolate, but Thr1172Ile was found in 11 (1.7%) isolates, respectively [38]. However, non-synonymous SNPs (nsSNPs) in the PE_PGRS33 genes were not observed in the XDR MTB strains in the present study. Also, previously, it has been observed that a Gly686Asp in PE_PGRS26 genes was observed in 20 (10%) MTB clinical strains belonging to the principal genetic group (PGG2), while Gly1122Gly in the PE_PGRS26 genes was observed in 1 (0.5%) of the MTB clinical strains also belonging to PGG2 [18]. However, this study did not observe nsSNPs in the PE_PGRS26 genes of XDR MTB strains.

In addition to SNPs, deletions have also been shown in the PE_PGRS genes 16, 26 and 33. In the XDR strains studied here, a 9bp DEL was observed in the PE_PGRS16 gene sequence of 2 (25%) XDR Other lineage 1 MTB strains belonging to PGG1 strains. Previously, in the PE_PGRS16 gene sequence, a 3bp deletion in PGG3 group strains and a 252bp deletion in three PGG2 group strains have been reported [18]. Also, in the PE_PGRS26 gene, both 3bp and 150 bp DELs have been reported in PGG2 group strains and PGG1 group strains [18]. In this study, 2 (9.5%) CAS1 MTB strains showed 9bp DELs in the PE_PGRS26 gene belonging to the PGG1 group. It was observed that 1-9bp DELs were present in the PE_PGRS33 gene in EAI (100%)

and Other lineage 1 (28.57%). This correlates with previous work which has 3 bp, 9 bp and 273 bp, respectively, in the PE_PGRS33 gene of MTB strains [38].

In this study, the variable 18bp INS in PE_PGRS26 and 9bp INS PE_PGRS33 was observed. INS of 9bp and 18bp have been reported in the PE_PGRS26 gene [18].

Overall, this work demonstrates the variability in the genome of MTB clinical strains. As these PE_PGRS genes contribute to immunogenicity, the variations in XDR strains may be associated with their ability to persist within the host.

Conclusion: Multiple DELs and INS were observed in the PE_PGRS genes in CAS1 XDR–MTB strains. As these strains are predominant in this endemic region, it indicates a need to further understand the functions of the PE_PGRS genes and its persistence.

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Competing interest: Authors declare that they have no competing interests.

Ethical approval: This work received approval from the Ethical Review Committee of the Aga Khan University.

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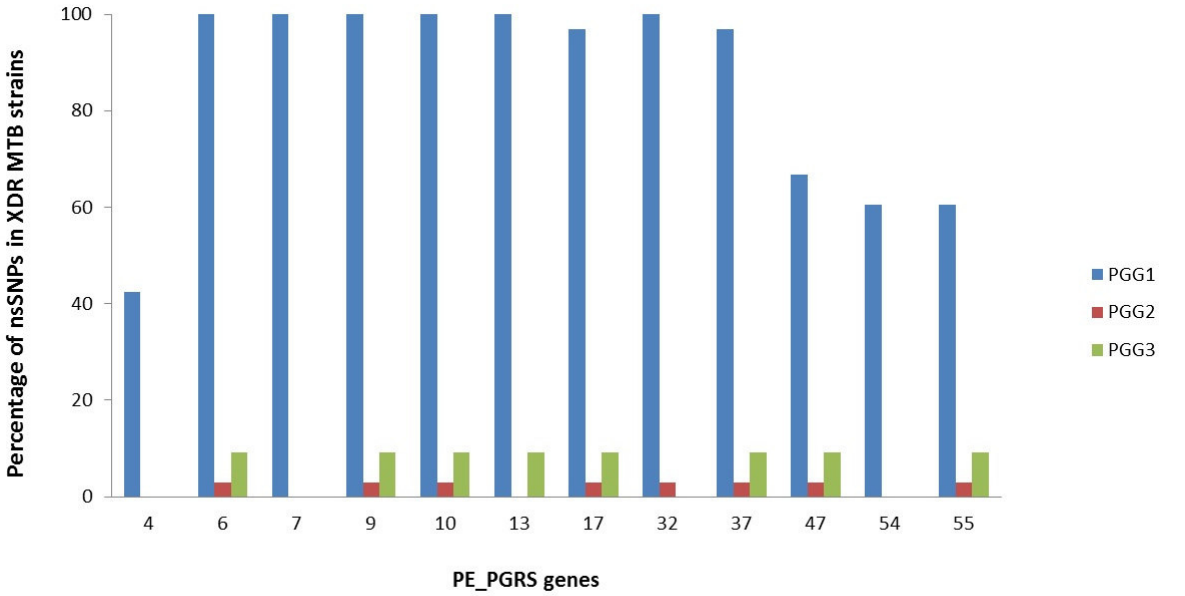


Table 1. The detection of PE_PGRS gene copies in XDR *M. tuberculosis* strains

		Lineage 1						Lineage 3																													Lineage 4			
		EAI		Other lineage 1				CAS1																				CAS	CAS2	Other lineage 3				T1			X3
PE_PGRS	REF	X5	X32	X17	X49	X57	X6	X7	X8	X10	X11	X12	X13	X14	X16	X21	X33	X37	X39	X40	X42	X43	X44	X47	X48	X55	X61	X18	X22	X4	X1	X9	X45	X60	X41	X56	X58	X46
1	**1**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	**2**	1	2	-	1	-	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	-	2	2	-	2	-	-	2	-	2	2	2	2	-	-	-	2
3	**4**	3	4	4	4	3	2	4	2	2	2	3	2	3	1	4	3	3	4	4	3	2	4	3	3	4	3	3	3	3	3	2	3	2	2	3	3	3
4	**11**	6	7	9	8	8	7	10	8	10	6	10	11	11	4	11	10	11	10	6	9	11	10	10	9	7	11	10	11	11	9	9	11	10	8	8	1	5
6	**3**	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	2	2	2
7	**3**	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1	2
9	**7**	7	7	7	6	7	7	7	6	7	7	6	6	7	5	7	6	6	6	6	6	6	6	7	7	6	6	7	6	6	6	6	7	7	5	5	5	5
10	**8**	7	7	6	7	7	8	8	8	8	8	8	8	8	6	8	8	8	8	8	8	8	8	8	8	8	7	7	8	6	8	8	8	8	8	7	7	7
13	**3**	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	2	2	1
14	**1**	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15	**1**	-	-	-	-	-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	-
17	**2**	2	2	2	2	2	2	2	2	1	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	1	1	1	1
18	**4**	3	3	3	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	-	-	-	-
19	**1**	-	-	-	-	-	1	1	1	1	1	1	1	1	1	1	1	-	-	1	1	1	1	1	-	1	-	1	1	1	1	-	1	1	-	-	-	-
20	**1**	-	-	-	-	-	1	1	1	-	1	-	1	1	1	-	-	-	-	-	-	-	-	-	1	-	-	-	1	-	1	-	-	-	-	-	-	1
21	**3**	-	-	-	-	-	3	3	3	3	3	3	-	3	3	3	-	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	-	-	-	-
24	**2**	-	-	-	-	-	2	2	2	2	2	2	2	2	2	-	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	-	-	-	-
25	**1**	1	1	1	1	1	1	1	1	1	1	1	1	1	-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	1
26	**2**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-	1	1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	-
27	**3**	2	2	-	2	1	2	3	3	3	3	1	3	3	3	3	3	3	3	3	3	3	3	3	2	3	3	3	3	3	3	2	3	3	-	-	2	-
28	**8**	4	2	1	-	1	7	6	6	8	6	5	7	6	3	5	2	5	4	3	3	3	3	5	6	3	5	5	6	6	4	5	5	7	2	1	4	4
30	**1**	-	-	-	-	-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	-
32	**1**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	1
33	**1**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-	1	1	1	1	1	1	-	-	-	1
36	**1**	-	-	-	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
37	**1**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
38	**2**	-	-	-	-	-	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	-	2	2	2	2	2	-	-	-	-
43	**2**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
45	**2**	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	-	-	-	-
46	**1**	-	-	-	-	-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	-
47	**3**	3	3	2	3	3	3	3	3	3	3	3	3	3	2	2	3	3	3	3	3	3	3	3	3	3	2	2	3	3	3	3	3	2	2	2	2	3
48	**1**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	1
49	**1**	-	-	-	-	-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	-
50	**2**	-	-	-	-	-	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	2	1	2	2	2	2	2	2	2	2	2	-	-	-	-
51	**1**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
53	**3**	1	1	-	-	1	1	-	-	1	1	-	1	1	-	1	-	1	-	-	1	-	-	-	1	-	1	1	-	-	1	1	1	-	-	-	-	-
54	**5**	2	2	2	3	3	4	2	4	4	2	3	2	3	1	4	-	2	2	2	1	3	2	2	2	1	2	4	2	3	3	3	3	2	-	-	2	1
55	**4**	3	3	3	3	3	3	1	3	3	1	3	1	2	1	3	1	1	1	1	1	1	-	1	1	1	1	1	3	2	2	2	1	3	1	1	1	1
56	**2**	2	2	2	2	2	-	-	-	2	-	2	-	-	-	2	-	-	-	-	-	-	-	-	-	-	2	2	2	-	-	-	-	-	-	-	-
57	**4**	1	2	2	2	1	1	1	2	1	1	2	2	2	1	3	1	-	2	3	2	3	2	-	1	1	3	1	-	1	1	1	2	2	-	-	-	-
59	**1**	1	1	-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	1
62	**1**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

CAS1: Central Asian Strain 1, EAI: East African Indian, OPN: Orphan, T1: undefined group, X family

*The dashes denotes no information of PE_PGRS gene copies in XDR MTB strains

Table 2. The detection of SNPs in PE_PGRS genes of XDR *M. tuberculosis* strains

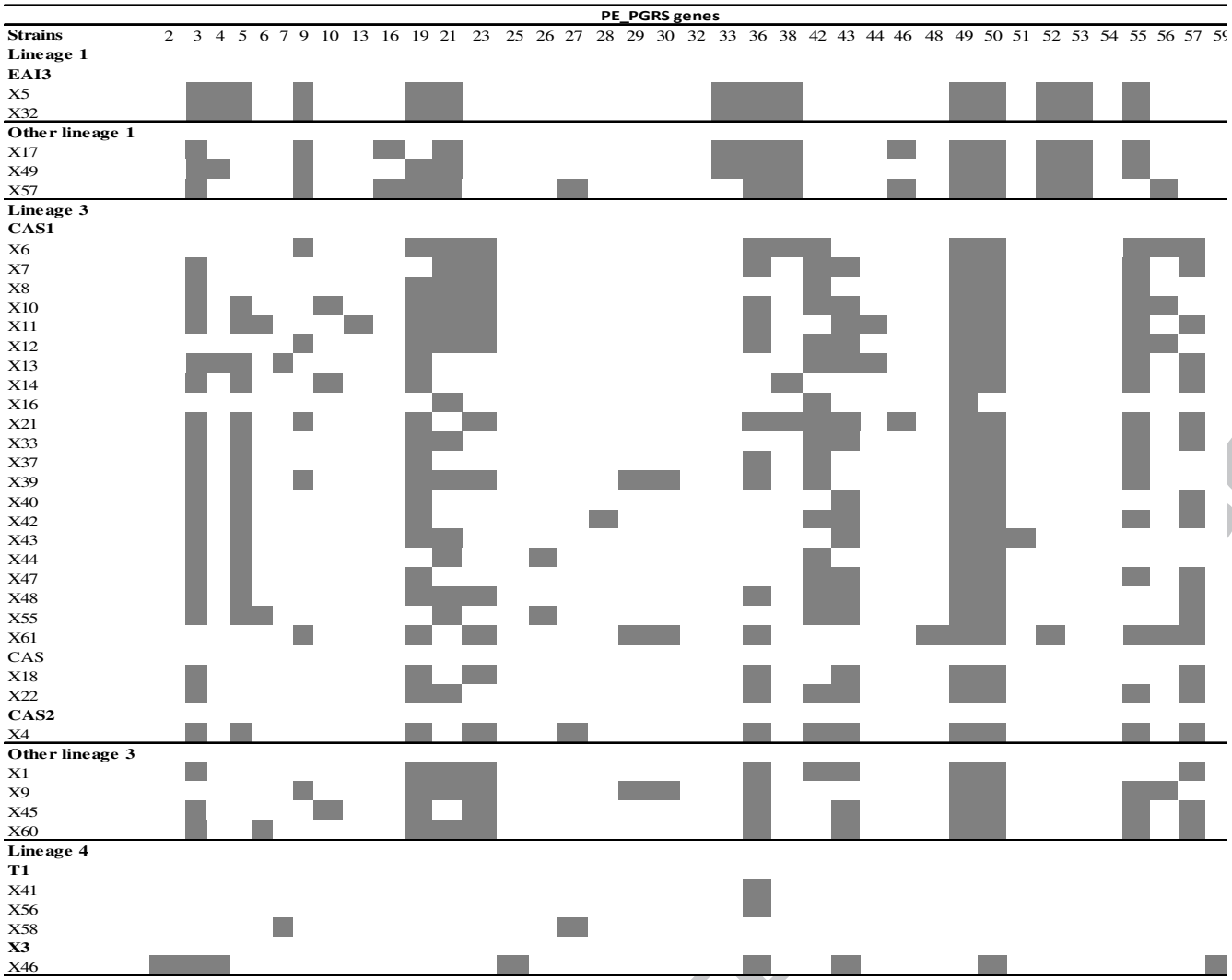
		Lineage 1					Lineage 3																												Lineage 4						
		EAI		Other lineage1			CAS1																					CAS	CAS2		Other lineage3				T1			X3			
POS	REF	X5	X32	X17	X49	X57	X6	X7	X8	X10	X11	X12	X13	X14	X16	X21	X33	X37	X39	X40	X42	X43	X44	X47	X48	X55	X61	X18	X22	X4	X1	X9	X45	X60	X41	X56	X58	X46	S/NS	AA Change	GENE
132417	**C**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	S	R	PE_PGRS1
150896	**C**	G	G	-	G	-	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	G	G	-	G	-	-	G	-	G	G	G	G	-	-	-	G	S	P	PE_PGRS2
150897	**C**	-	G	-	-	-	-	G	G	G	G	G	G	G	A,T	G	G	G	G	G	G	-	G	G	-	G	-	-	G	-	G	G	G	G	-	-	-	G	S	P	PE_PGRS2
333892	**G**	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	S	F	PE_PGRS3
334641	**G**	-	C	C	C	C	-	C	-	-	-	-	-	-	-	C	-	-	C	C	-	-	C	-	C	C	-	-	-	-	-	-	-	-	-	-	-	-	S	A	PE_PGRS3
335971	**A**	G	G	G	G	G	G	G	G	G	G	G	-	G	-	G	G	G	G	G	G	G	G	G	-	G	G	G	G	G	G	G	G	-	-	G	G	G	S	P	PE_PGRS3
336005	**G**	A	A	A	A	-	-	A	-	-	-	A	A	A	-	A	A	A	A	A	A	-	A	A	A	A	A	A	A	A	A	-	A	A	A	A	A	A	S	I	PE_PGRS3
336728	**G**	A	A	A	-	-	-	A	-	-	-	A	A	A	-	A	-	A	-	-	A	A	-	-	-	-	A	A	A	A	-	-	A	-	-	-	-	-	S	G	PE_PGRS4
337820	**G**	A	A	A	A	A	A	A	A	A	A	A	A	A	T	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	-	-	S	G	PE_PGRS4
338020	**A**	C	C	C	C	C	-	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	-	C	S	V	PE_PGRS4
338100	**T**	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	-	C	S	N	PE_PGRS4
338453	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	G	S	A	PE_PGRS4
338618	**C**	-	-	-	-	-	-	-	-	G	G	G	G	G	-	G	G	G	G	G	G	G	G	G	-	G	G	-	G	G	-	G	G	G	-	-	G	G	S	G	PE_PGRS4
338648	**T**	-	-	-	-	-	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	-	-	-	S	G	PE_PGRS4
338876	**G**	-	A	A	A	A	-	A	-	A	-	-	A	A	-	A	A	A	A	-	A	A	A	A	A	A	A	A	A	A	A	-	A	A	A	A	-	-	NS	S to R	PE_PGRS4
338903	**G**	C	C	C	C	C	C	C	C	C	-	C	C	C	-	C	C	C	C	-	C	C	C	C	C	-	C	C	C	C	C	C	C	C	C	C	-	C	S	A	PE_PGRS4
338960	**T**	-	-	C	C	C	C	C	C	C	-	C	C	C	-	C	C	C	C	-	-	C	C	C	C	-	C	C	C	C	C	C	C	C	C	C	-	-	S	A	PE_PGRS4
338963	**T**	-	-	C	C	C	C	C	C	C	-	C	C	C	-	C	C	C	C	-	-	C	C	C	C	-	C	C	C	C	C	C	C	C	C	C	-	-	S	T	PE_PGRS4
623163	**C**	-	-	-	-	-	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	-	-	-	S	A	PE_PGRS6
623472	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	NS	D to E	PE_PGRS6
623508	**C**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	S	A	PE_PGRS6
672491	**C**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	S	G	PE_PGRS7
673238	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	-	-	G	NS	H to Q	PE_PGRS7
674702	**A**	-	-	-	-	-	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	-	-	-	S	G	PE_PGRS7
836426	**A**	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	S	G	PE_PGRS9
836454	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	S	T	PE_PGRS9
836658	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	S	T	PE_PGRS9
837033	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	NS	N to K	PE_PGRS9
837911	**T**	G	G	G	G	G	G	G	G	G	G	G	G	G	-	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	-	-	-	S	G	PE_PGRS9
837915	**G**	A	A	A	-	A	A	A	-	A	A	-	-	A	-	A	-	-	-	-	-	-	-	A	A	-	-	A	-	-	-	-	A	A	-	-	-	-	S	V	PE_PGRS9
839123	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	G	G	G	G	G	G	G	G	S	G	PE_PGRS10
839129	**C**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	G	G	G	G	G	G	G	G	S	E	PE_PGRS10
839194	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	S	T	PE_PGRS10
839334	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	S	K	PE_PGRS10
839348	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	NS	S to R	PE_PGRS10
840496	**C**	G	G	G	G	G	G	G	G	G	G	G	G	G	-	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G,A	G	G	G	G	S	G	PE_PGRS10
840847	**C**	-	-	-	-	-	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	-	-	-	S	G	PE_PGRS10
925453	**C**	-	-	-	-	-	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	-	-	-	S	A	PE_PGRS13
927110	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	NS	S to R	PE_PGRS13
927385	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	S	G	PE_PGRS13
929128	**C**	-	-	-	-	-	-	-	-	G	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S	G	PE_PGRS14
969762	**C**	-	-	-	-	-	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	-	-	-	S	G	PE_PGRS15
1093406	**A**	G	G	G	G	G	G	G	G	C	G	G	G	G	-	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	NS	V to L	PE_PGRS17
1093907	**T**	C	C	C	C	C	C	C	C	-	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	-	C	C	C	C	C	C	C	C	-	-	-	-	S	G	PE_PGRS17
1095490	**A**	-	-	-	-	-	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	-	-	-	S	V	PE_PGRS18
1095644	**C**	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	-	-	-	S	A	PE_PGRS18
1095678	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	-	-	-	S	A	PE_PGRS18
1095981	**A**	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	-	-	-	-	S	A	PE_PGRS18
1188985	**G**	-	-	-	-	-	A	A	A	A	A	A	A	A	A	A	-	-	A	A	A	A	A	-	A	-	A	A	A	A	-	A	A	-	-	-	-	-	S	G	PE_PGRS19
1191497	**T**	-	-	-	-	-	A	A	A	-	A	-	A	A	A	-	-	-	-	-	-	-	-	-	A	-	-	-	A	-	A	-	-	-	-	-	-	A	S	T	PE_PGRS20
1212624	**C**	-	-	-	-	-	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	T	T	T	T	T	T	T	-	-	-	-	S	G	PE_PGRS21
1212626	**A**	-	-	-	-	-	C	C	C,T	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	-	-	C	C	C	C	C	C	-	-	-	-	S	D	PE_PGRS21
1212971	**T**	-	-	-	-	-	C	C	C	C	C	C	-	C	C	C	-	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	-	-	-	-	S	V	PE_PGRS21
1488428	**C**	-	-	-	-	-	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	-	-	-	S	G	PE_PGRS24
1489142	**C**	-	-	-	-	-	T	T	T	T	T	T	T	T	T	-	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	-	-	-	S	G	PE_PGRS24
1573660	**T**	G	G	G	G	G	G	G	G	G	G	G	G	G	-	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	-	-	G	S	R	PE_PGRS25
1618633	**G**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S	A	PE_PGRS26
1618978	**T**	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	-	C	C	C	C	C	C	C	C	C	C	C	C	C	-	-	-	-	S	D	PE_PGRS26
1634418	**C**	-	-	-	-	A		T	T	T	T	-	T	T	T	T	T	T	T	T	T	T	T	T	-	T	T	T	T	T	T	-	T	T	-	-	-	-	S	A	PE_PGRS27
1634609	**C**	T	T	-	T	-	T	T	T	T	T	-	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	-	T	-	S	A	PE_PGRS27
1634610	**C**	T	T	-	T	-	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	-	T	-	S	V	PE_PGRS27
1636826	**C**	A	A	A	-	A	A	A	A	A	A	-	A	A	A	A	A	A	A	A	A	A	A	-	A	A	A	A	A	A	A	A	A	A	A	A	A	A	S	G	PE_PGRS28
1636918	**C**	T	T	-	-	-	-	-	-	T	-	-	T	-	-	T	T	T	T	-	-	-	-	-	-	-	T	-	-	-	-	T	T	T	T	-	-	T	S	G	PE_PGRS28
1636980	**G**	-	-	-	-	-	T	T	T	T	T	T	T	T	-	T	-	-	-	-	-	-	-	T	T	-	-	T	T	T	-	-	T	T	-	-	T	T	S	P	PE_PGRS28
1636981	**G**	-	-	-	-	-	T	T	T	T	T	T	T	T	-	T	-	-	-	-	-	-	-	T	T	-	-	T	T	T	-	-	T	T	-	-	T	-	S	G	PE_PGRS28
1636983	**C**	-	-	-	-	-	G	G	G	G	G	-	G	G	-	-	-	-	-	-	-	-	-	G	G	-	-	G	G	G	G	-	G	G	-	-	G	G	S	G	PE_PGRS28
1636996	**G**	C	-	-	-	-	C	-	-	C	-	C	-	-	-	-	-	C	C	-	-	-	-	-	-	-	C	-	-	-	-	C	-	-	-	-	-	-	S	R	PE_PGRS28
1638182	**C**	T	-	-	-	-	T	T	T	T	T	T	T	T	T	T	-	T	-	T	T	T	T	T	T	T	T	T	T	T	T	T	-	T	-	-	-	-	S	S	PE_PGRS28
1638194	**G**	-	-	-	-	-	C	C	C	C	C	C	C	C	C	-	-	C	C	C	C	C	C	C	C	C	C	-	C	C	C	C	-	C	-	-	-	-	S	A	PE_PGRS28
1863584	**G**	-	-	-	-	-	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	-	-	-	S	T	PE_PGRS30
2045310	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	-	-	G	NS	I to M	PE_PGRS32
2061958	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	G	G	G	G	G	G	-	-	-	G	S	A	PE_PGRS33
2357324	**C**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S	A	PE_PGRS36
2387733	**T**	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	-	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NS	E to D	PE_PGRS37
2424114	**C**	-	-	-	-	-	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	-	A	A	A	A	A	-	-	-	-	S	R	PE_PGRS38
2424151	**C**	-	-	-	-	-	A	A	A	A	A	A	A	-	A	A	A	A	A	A	A	A	A	A	A	A	A	A	-	A	A	A	A	A	-	-	-	-	S	A	PE_PGRS38
2803025	**T**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S	D	PE_PGRS43
2943675	**G**	-	-	-	-	-	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	-	-	-	-	S	G	PE_PGRS45
2944515	**A**	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	-	-	-	-	S	G	PE_PGRS45
2960592	**C**	-	-	-	-	-	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	-	-	-	S	G	PE_PGRS46
3054081	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	-	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	-	-	G	S	G	PE_PGRS47
3054321	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	S	G	PE_PGRS47
3054724	**A**	G	G	-	G	G	G	G	G	G	G	G	G	G	G	-	G	G	G	G	G	G	G	G	G	G	-	-	G	G	G	G	G	-	G	G	G	G	NS	S to R	PE_PGRS47
3162805	**C**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	-	-	G	S	R	PE_PGRS48
3738364	**G**	-	-	-	-	-	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	-	-	-	-	S	V	PE_PGRS49
3740181	**T**	-	-	-	-	-	C	C	C	C	C	C	C	C	C	C	C	-	C	C	-	C	C	C	C	C	C	C	C	C	C	C	C	C	-	-	-	-	S	N	PE_PGRS50
3741240	**C**	-	-	-	-	-	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	-	T	T	T	T	T	T	T	T	T	-	-	-	-	S	G	PE_PGRS50
3780031	**C**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S	H	PE_PGRS51
3929075	**G**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S	G	PE_PGRS53
3929084	**C**	G	G	-	-	G	G	-	-	G	G	-	G	G	-	G	-	G	-	-	G	-	-	-	G	-	G	G	-	-	G	G	G	-	-	-	-	-	S	A	PE_PGRS53
3930526	**G**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S	G	PE_PGRS53
3934421	**C**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S	I	PE_PGRS54
3934542	**T**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	-	G	G	S	S	PE_PGRS54
3934699	**G**	A	A	A	A	A	A	-	A	A	A	A	-	A	-	A	-	A	A	A	-	A	A	A	A	-	A	A	A	A	A	A	A	A	-	-	A	-	NS	S to R	PE_PGRS54
3934897	**T**	-	-	-	-	-	C	-	C	C	-	-	-	-	-	C	-	-	-	-	-	-	-	-	-	-	C	C	-	-	-	-	-	-	-	-	-	-	S	F	PE_PGRS54
3940802	**A**	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	G	G	G	-	G	G	G	G	-	G	G	G	G	G	G	NS	N to K	PE_PGRS55
3940965	**G**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S	G	PE_PGRS55
3941497	**G**	C	C	C	C	C	C	-	C	C	-	C	-	-	-	C	-	-	-	-	-	-	-	-	-	-	-	-	C	C	C	C	-	C	-	-	-	-	S	G	PE_PGRS55
3941499	**C**	A	A	A	A	A	A	-	A	A	-	A	-	A	-	A	-	-	-	-	-	-	-	-	-	-	A	-	A	-	-	A	-	A	-	-	-	-	S	A	PE_PGRS55
3941834	**G**	C	C	C	C	C	-	-	-	C	-	C	-	-	-	C	-	-	-	-	-	-	-	-	-	-	C	C	C	-	-	-	-	-	-	-	-	-	S	G	PE_PGRS56
3941836	**C**	A	A	A	A	A	-	-	-	A	-	A	-	-	-	A	-	-	-	-	-	-	-	-	-	-	A	A	A	-	-	-	-	-	-	-	-	-	S	A	PE_PGRS56
3946879	**C**	-	G	-	-	-	-	-	-	-	-	-	-	-	-	G	-	-	-	G	-	G	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S	L	PE_PGRS57
3947395	**G**	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	-	A	A	A	A	A	-	A	A	A	-	-	A	A	-	A	-	-	-	-	-	S	G	PE_PGRS57
3948337	**G**	-	-	-	T	-	-	-	A	-	-	-	A	A	-	A	-	-	A	A	A	A	A	-	-	-	A	A	-	-	-	-	A	A	-	-	-	-	S	G	PE_PGRS57
3949001	**G**	-	-	G	-	-	-	-	-	-	-	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	A	-	A	-	-	-	-	S	A	PE_PGRS57
4037283	**T**	G	G	-	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	-	-	-	G	S	G	PE_PGRS59
4277259	**A**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	G	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NS	N to K	PE_PGRS62

CAS1: Central Asian Strain 1, EAI: East African Indian, OPN: Orphan, T1: undefined group, X family

*The dashes denotes no information of SNPs in the PE_PGRS genes of XDR MTB strains

denotes, synonymous (sSNPs) or non-synonymous (nsSNPs)

Table 3. The detection of deletions in PE_PGRS genes of XDR *M. tuberculosis* strains

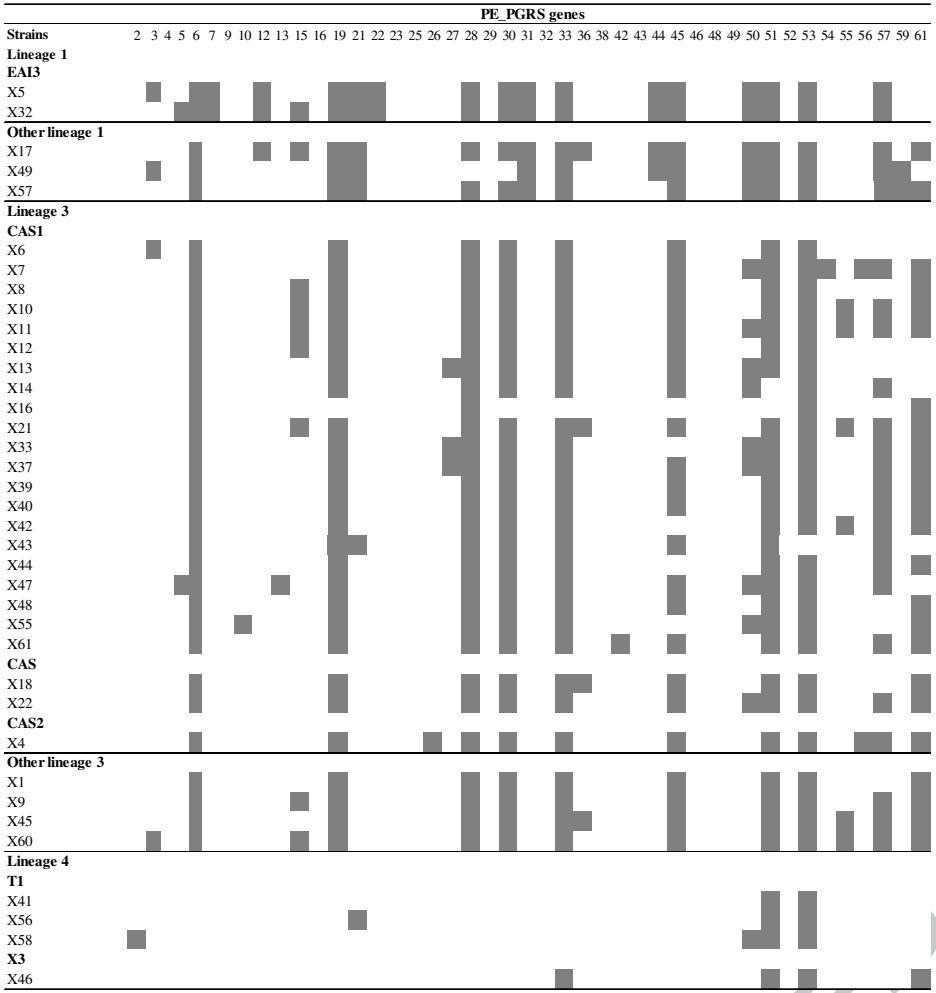


CAS1: Central Asian Strain 1, EAI: East African Indian, T1: undefined group, X3: X family

*The shaded portion denotes deletions in the PE_PGRS genes

#The unshaded portion denotes absence of deletions in the PE_PGRS genes

Table 4. The detection of insertions in PE_PGRS genes of XDR *M. tuberculosis* strains



CAS1: Central Asian Strain 1, EAI: East African Indian, T1: undefined group, X3: X family

*The shaded portion denotes deletions in the PE_PGRS genes

#The unshaded portion denotes absence of insertions in the PE_PGRS genes