

Supplemental Table S1: Single-nucleotide polymorphisms detected in the *pncA* gene, by country and resistance phenotype.

SNP location	SNP type	Codon Change	Country and reference	Phenotype linked to SNP	Total Frequency	Sensitive Frequency (%)
-125	C insertion	Upstream	Europe (76)	S	4	100%
-125 & 195	C insertion & C>T	Upstream & Ser65Ser	Europe (76)	S	11	100%
-124 & 195	C deletion & C>T	Upstream & Ser65Ser	Europe (76)	S	1	100%
-33	G insertion	Upstream	Sweden (40)	S	1	100%
-13	G>T	Upstream	Canada (73), Europe (76)	R (73), S (76)	2	50%
-7	T>C	Upstream	Korea (6), USA (35), Thailand (55), Europe (76)	S (6), N/S (55), R (35,76)	8	12.5%
-3	C insertion	Upstream	Sweden (40,61), Europe (76)	S (40,76), *R/S (61)	4 (r/s – multicentre study)	75%
14	T>C	Ile5Thr	China (72)	S	1	100%
16	A>C	Ile6Leu	Europe (76)	S	128	100%
27	G>C	Val9Val	Peru (14)	S	1	100%
31	A>G	Asn11Asp	China (72)	S	1	100%
35	A>C	Asp12Ala	Cambodia (5), USA (13), China (16,50,72), Japan (20), Korea (7,21), India (27,62), Mexico (28), Peru (34), Canada (73), Europe (76)	N/S (5,27), R (7,13,16,20,21,28,34,50,62,73,76), S (72)	28	7%
35	A>G	Asp12Gly	South Africa (3), Europe (76)	R (3), S (76)	11	18%
40	T>G	Cys14Gly	Korea (21), Peru (34), Belgium (45)	S (21,45), R (34)	5	20%
49	G>T	Gly17Cys	Kazakhstan (77)	S	1	100%
62	T>C	Val21Ala	Germany (75), Europe (76)	N/S (75), S (76)	5	80%
82	G>A	Ala28Thr	Netherlands (43)	S	1	100%
92	T>C	Ile31Thr	Thailand (9,55)	*R/S (9), N/S (55)	21	43%
92	T>G	Ile31Ser	Thailand (9), Europe (76)	*R/S (9), R (76)	5	20%
98	A>C	Asp33Ala	Taiwan (19), China (36)	S (19), R (36)	2	50%
104	T>C	Leu35Pro	Thailand (9), India (27), China (36), Japan (49), Spain (63), Europe (76)	R (9,49,63,76), N/S (27), S (36)	6	17%
104	T>G	Leu35Arg	Brazil (24), China (72)	R (24), S (72)	2	50%
114	G>C	Ala38Ala	Europe (76)	S	1	100%
117	2-bp insertion	Frameshift	Korea (6)	S	1	100%
127	C>T	His43Tyr	Netherlands (43)	S	1	100%
134	T>C	Val45Ala	Thailand (9), China (36), Europe (76)	R (9,36), S (76)	3	33%
137	C>T	Ala46Val	Portugal (10), Canada (13,73), USA (13), Korea (13,21), Yemen (23), China (72), Europe (76)	R (10,13,23,73), S (21,72,76)	13	23%
139	A>G	Thr47Ala	Korea (7), Mexico (28), China (33), USA (35,41,71), Sweden (40,67), Europe (76)	R (7,28,33,40,41), S (35,67,71,76)	50	80%
143	A>C	Lys48Thr	Korea (6), Peru (34), Cuba (60), Europe (76)	S (6), R (34,60,76)	10	10%
146	A>C	Asp49Ala	Korea (7,21), Brazil (24), Belgium (45), Japan (49), Europe (76)	R (7,21,45,49,76), *R/S (24)	8	12.5%
147	C>G	Asp49Glu	Brazil (24), Netherlands (43)	S (24,43)	2	100%
188	A>C	Asp63Ala	Mexico (28), Belgium (45), China (51), Russia (65), Singapore (69), Europe (76)	R (28,45,69,76), S (51), N/S (65)	9	11%
191	A>C	Tyr64Ser	Belgium (45), Europe (76)	S (45), *R/S (76)	3	67%
193	T>C	Ser65Pro	China (72)	S	1	100%
195	C>T	Ser65Ser	Iran (2), South Africa (3,66), Japan (20), India (27,53,64), Sweden (40,61,67), USA (41), Tanzania (55), Canada (73), Europe (76)	R (2), S (3,20,40,41,53,61,64,66,67,73,76), N/S (27,55)	76	70%

195 & 152	C>T & A>G	Ser65Ser & His51Arg	India (64)	S	1	100%
199	T>C	Ser67Pro	Korea (6,7), Thailand (9), Canada (23), Sweden (40), China (50,51), Canada (73), Europe (76)	R ^{7,9,23,40,50,51,73,76} , S (6)	10	10%
201	TCG insertion	Frameshift	China (72)	S	1	100%
234	C>T	Gly78Gly	China (51)	S	1	100%
245	A>G	His82Arg	USA (13), Brazil (18), China (36,72), Belgium (45), New Zealand (48), Europe (76)	R (13,18,45,48,72,76), *R/S (36)	12	8%
277	G>A	Val93Met	Kazakhstan (77)	S	1	100%
290	G>A	Gly97Asp	South Africa (3), Japan (17), Taiwan (19,31), USA (35), China (36,72), New Zealand (48), Singapore (69), Europe (76)	R (3,17,19,31,35,36,48,69,76), S (72)	13	8%
304-306	GCG>AGA	Ala102Arg	Europe (76)	S	1	100%
304	G>C	Ala102Pro	Cambodia (5), Europe (76)	N/S (5), S (76)	3	33%
305	C>T	Ala102Val	South Africa (3,66), Russia (4), China (36,72), Europe (76)	R (3,4,36,66), S (72,76)	10	40%
309	C>G	Tyr103STOP	Russia (4), Korea (7,21), Brazil (18), South Africa (25), Peru (34), USA (35), Europe (76)	R (4,7,18,25,34,35,76), S (21)	17	6%
341	C>T	Thr114Met	South Africa (25)	S	10	100%
347	T>C	Leu116Pro	Peru (34), Italy (42), China (72), Europe (76)	R (34,42,76), *R/S (72)	5	20%
371	G>A	Gly124Asp	Netherlands (43)	S	1	100%
382	G>T	Val128Phe	China (72)	S	1	100%
389	T>C	Val130Ala	Korea (1,21), China (36,50), Europe (76)	R (1,36,50,76), S (21)	5	20%
401	C>T	Ala134Val	Canada (13), Peru (14), Taiwan (19,31), USA (35), Russia (65), China (72), Europe (76)	R (13,14,19,31,35,76), N/S (65), S (72)	9	11%
403	A>C	Thr135Pro	Korea (1,7,8,21), China (33), Peru (34), USA (35), Belgium (45), Japan (49), Cuba (60), Poland (75), Europe (76)	R (1,7,8,21,33,34,35,49,75,76), S (45,60)	41	5%
404	C>G	Thr135Ser	Europe (76)	S	1	100%
407	A>G	Asp136Gly	Cambodia (5), Korea (8,21), South Africa (25), China (33,72), Peru (34), Thailand (55), Europe (76)	N/S (5,55), R (8,21,25,33,72), S (34,76)	11	27%
410	A>G	His137Cys	USA (35), Europe (76)	R (35), S (76)	4	50%
419	G>A	Arg140His	Japan (15), South Korea (47)	S (15), N/S (47)	3	66%
419 & 493	G>A & G>A	Arg140His & Ala165Thr	Japan (15)	S	2	100%
419 & 450 & 493	G>A & C>A & G>A	Arg140His & Gly150Gly & Ala165Thr	Japan (15)	S	1	100%
427	G>A	Ala143Thr	Iran (2), Belgium (45), Europe (76)	R (2), S (45,76)	4	75%
460	A>G	Arg154Gly	Korea (1), South Africa (3,66), Russia (4), China (36,72), Europe (76)	R (1,3,4,36,66), S (72), *R/S (76)	8	25%
462	G>T	Arg154Ser	Europe (76)	S	3	100%
464	T>C	Val155Ala	Korea ^{6,21} , Peru (14), China ⁷²	S (6,72), N/S (14), *R/S (21)	6	66%
470	T>G	Val157Gly	Korea (1), China (72), Europe (76)	R (1,76), S (72)	4	25%
475	C>G	Leu159Val	Europe (76)	S	1	100%
478	A>G	Thr160Ala	China (72), Europe (76)	S (72), R (76)	2	50%
503	C>T	Thr168Ile	Europe (76)	S	2	100%
511	G>A	Ala171Thr	Portugal (10), Bangladesh (11), USA (35), China (72)	R (10,11,35), S (72)	4	25%
512	C>T	Ala171Val	Scotland (11), China (72), Canada (73), Europe (76)	S (11,76), *R/S (72), R (73)	6	67%
521	A>G	Glu174Gly	China (33,54)	R (33), S (54)	2	50%

523	A>G	Met175Val	Japan (20), Brazil (24), China (36), Belgium (45), Thailand (55), Poland (75), Europe (76)	R (20,24,45,75,76), S (36), N/S (55)	14	7%
525	G>A	Met175Ile	Korea (6), China (33), Belgium (45), Brazil (57), Europe (76)	S (6), *R/S (45), R (33,57,76)	15	13%
529	A>C	Thr177Pro	Taiwan (19), China (36)	R (19), S (36)	2	50%
545	T>C	Leu182Ser	Korea (21), France (39), Europe (76)	S (21), R (39,76)	3	33%
545	T>G	Leu182Trp	Europe (76)	S	1	100%
559	T>G	STOP187Gly	India (53), Sweden (61)	R (53), S (61)	2	50%
559	T>C	STOP187Arg	China (72)	S	1	100%

Abbreviations: Ala, Alanine; Arg, Arginine; Asn, Asparagine; Asp, Aspartate; bp, base pair; Cys, Cysteine; Glu, Glutamate; Gln, Glutamine; Gly, Glycine; His, Histidine; Ile, Isoleucine; Leu, Leucine; Lys, Lysine; Met, Methionine; N/S, not stated; Phe, Phenylalanine; Pro, Proline; R, resistant; S, susceptible; Ser, Serine; SNP, single-nucleotide polymorphism; Thr, Threonine; Trp, Tryptophan; Tyr, Tyrosine; Val, Valine. * Article reported one isolate sensitive and one isolate resistant.

We searched PubMed, ScienceDirect and Scopus on July 14, 2014 for relevant articles published in the English language between 1998 and 2014 using an *a priori* protocol. The search terms “tuberculosis AND (pyrazinamide OR PZA) AND (phenotype OR genotype OR PZase OR pyrazinamidase OR *pncA* OR BACTEC OR mutations OR resistance OR resistant OR susceptibility OR sequence analysis OR microbial sensitivity tests OR molecular typing)” were used to identify articles reporting on PZA resistance using any of the methods of interest: phenotypic PZA DST, PZase activity assays, and/or genotypic PZA assays. Additional articles were identified from reference lists and review articles. Studies were eligible for inclusion if they performed genotypic testing using polymerase chain reaction (PCR) or DNA sequencing and characterized the found SNPs. The characterized SNPs also needed to have a phenotypic result, only phenotypic results from the BACTEC liquid-based DST 460 or 960, considered the reference standard for PZA DST, or PZase activity assays using classic or modified Wayne’s methods were considered.

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