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Prevalence of *Mycobacterium tuberculosis* mutations associated with isoniazid and rifampicin resistance: A systematic review and *meta*-analysis

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ABSTRACT

Tuberculosis (TB) is still one of the leading causes of worldwide death, especially following the emergence of strains resistant to isoniazid (INH) and rifampicin (RIF). This study aimed to systematically review published articles focusing on the prevalence of INH and/or RIF resistance-associated mutations of *Mycobacterium tuberculosis* isolates in recent years. Literature databases were searched using appropriate keywords. The data of the included studies were extracted and used for a random-effects model *meta*-analysis. Of the initial 1442 studies, 29 were finally eligible to be included in the review.

The overall resistance to INH and RIF was about 17.2% and 7.3%, respectively. There was no difference between the frequency of INH and RIF resistance using different phenotypic or genotypic methods. The INH and/or RIF resistance was higher in Asia. The S315T mutation in KatG (23.7 %), C-15 T in InhA (10.7 %), and S531L in RpoB (13.5 %) were the most prevalent mutations. Altogether, the results showed that due to S531L in RpoB, S315T in KatG, and C-15 T in InhA mutations INH- and RIF-resistant *M. tuberculosis* isolates were widely distributed. Thus, it would be diagnostically and epidemiologically beneficial to track these gene mutations among resistant isolates.

1. Introduction

Tuberculosis (TB), a serious infections caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), is still one of the leading causes of death throughout the world [1,2]. The World Health Organization (WHO) annually reports the TB prevalence in the world. In 2019, it reported that 8.9 to 11 million people fell ill with TB, globally [1,3]. Recently, prevention and treatment of this deadly infection has received more special attention due to the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *M. tuberculosis* [4]. The MDR strains are at least resistant to isoniazid (INH) and rifampicin (RIF), which are the first-line antibiotics against TB [2,5].

Although the general drug resistance of *M. tuberculosis* is increasing all across the world, resistance to INH and RIF is of particular concern, since these are the first-line agents and both are used in conventional TB treatment. These two most potent anti-TB antibiotics have been used since the 1950 s [6]. With the introduction of isoniazid (also known as nicotinic acid hydrazide), which has the most potent anti-TB activity among all anti-TB drugs [7], TB became treatable [8]. Isoniazid inhibits the synthesis of mycolic acid, an important component of the *M. tuberculosis* cell wall [9]. Rifampicin (4-methyl-1-piperazinaminyl), is a lipophilic antibiotic with a broad spectrum of activity and the highest sterilizing activity [6]. Rifampicin inhibits the activity of RNA polymerase (*rpoB*) by binding the molecules to its β-subunit [10]. Although INH and RIF are currently the main anti-TB drugs, resistance to them is on the rise in many parts of the world [11].

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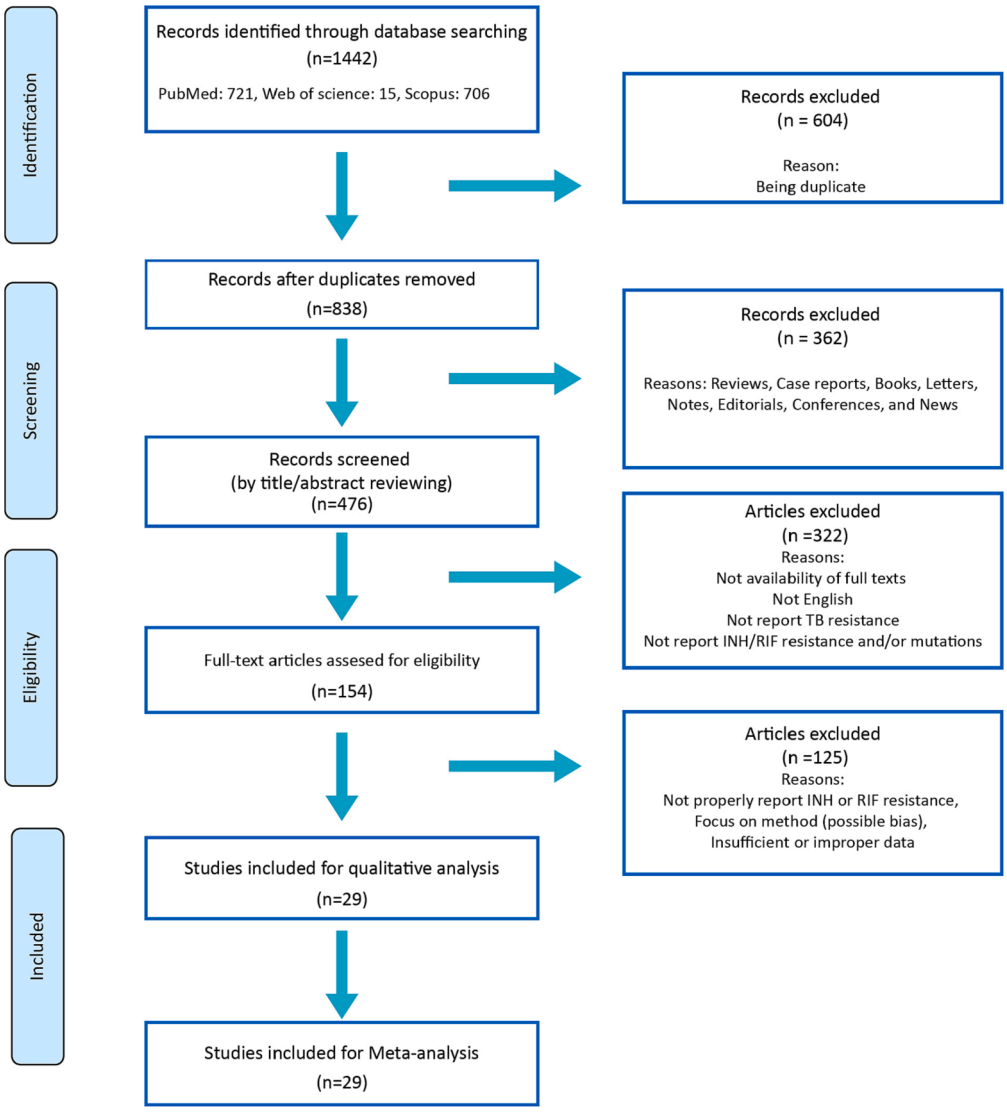

Fig. 1. Flowchart of the study strategy.

While it is well understood that patient nonadherence to treatment can lead to resistance, it is still unknown how host immune responses and antibiotic dynamics influence the development and selection of drug-resistant bacteria [11]. Genomic changes due to gene mutations are one of the well-known causes of drug resistance. As far as the resistance of *M. tuberculosis* to INH and RIF is concerned, it is frequently reported that mutations in some genes are the main causes of *M. tuberculosis* drug resistance. RIF resistance in *M. tuberculosis* can be explained by mutations in the *rpoB* gene, whereas INH resistance is linked to changes in the *katG*, *inhA*, *ahpC*, *kasA*, and *ndh* genes [12]. Although there are valuable reviews on TB prevalence and drug resistance of TB [6,13–19], more comprehensive reviews are required to shed more light on the prevalence of resistance to INH and RIF in clinical cases of *M. tuberculosis* and their associated gene mutations, particularly in recent years. Therefore, this study aimed to systematically review articles published worldwide on this topic from 2015 to 2020.

2. Materials and methods

2.1. The strategy of database searching

Four databases (Scopus, PubMed, Google Scholar, and Web of Science) were searched from Jan 2015 to Dec 2020 using the following keywords: "tuberculosis", "*Mycobacterium* spp.", "*Mycobacterium tuberculosis*", "*M. tuberculosis*", "Drug resistance", "Antibiotic resistance", "genes", "Isoniazid", "Rifampin", and "Rifampicin" alone or in combination with "AND'' and/or "OR'' operators. Preferred Reporting Items for Systematic Reviews and Meta-Analysis[1] (PRISMA) guideline was followed for the design of the study [20].

2.2. Eligibility criteria

Studies focusing on the frequency of mutations leading to INH and RIF resistance among *M. tuberculosis* isolates were included in this review. Letters, narrative/systematic reviews, and non-English studies were excluded. To remove any possible biases, the studies which focused on and aimed to introduce a specific detection/screening method were also excluded.

2.3. Study selection and data collection

The abstracts and full text of the retrieved studies were read carefully by two authors independently. The discrepancies were resolved through consulting with other authors. The following data were collected: the last name of the first author, publication year, sampling year, country, total sample size, status of cases (new or retreated), TB type (pulmonary

Table 1
The characteristics of the studies.

Study	Published year	Country	Sampling year	Study cases[a]	Tool sample No.	Total Mb No	New cases No.	Retreated	TB type No.		Drug sensitivity assay		Isolates Tested No[b]		Resistance to INH No.		Resistance to RIF No.		Reference
									PTB	EPTB	Phen.	Gen	Phen	Gen.	Phen	Gen.	Phen.	Gen.	
Al-Mutairi et al.	2019	Kuwait	-	S (RIF)	-	242	242	0	144	98	M	G&PCR	242	242	242	242	0	4	[43]
Alvarez et al.	2017	Spain	2004–2013	General	–	1861	1861	0	1499	362	P	G	1861	1861	60	42	7	7	[44]
Andreevskaya et al.	2017	Russia	2011–2014	General	–	1455	–	–	–	–	M&P	Biochip&Amplitub	1455	1455	968	–	829	–	[45]
Aung et al.	2015	Myanmar	2013–2013	General	212	191	191	0	191	0	P	G&PCR	191	189	44	43	35	33	[22]
Campelo et al.	2020	Brazil	2017–2018	R (Any)	110	41	41	0	41	0	M	PCR	41	41	37	36	37	33	[46]
Chaidir et al.-1	2015	Indonesia	2011–2012	General	–	199	147	52	199	–	–	–	–	199		19		14	[47]
Chaidir et al.-2	2019	Indonesia	2006–2015	General	–	322	270	52	216	106	P	WGS	102	322	17	29	7	10	[48]
Chatterjee et al.	2017	India	2004–2007, & 2014	General	–	74	61	13	69	5	M	WGS	29	74	13	34	12	30	[49]
Ennassiri et al.	2018	Morocco	2013–2015	R (Any)	–	319	88	231	319	0	–	G	–	318		173		116	[50]
Esteves et al.	2018	Brazil	2010	R (INH)	129	111	–	–	111	–	P	PCR	63	63	61	45	37	35	[51]
Faksri et al.	2019	Thailand	1998–2013	R + S (any)	–	266	–	–	212	54	P	WGS	261	266	204	198	202	187	[52]
Garzon-Chavez et al.	2019	Ecuador	2014–2016	R + S (any)	2275	380	–	–	–	–	–	–	380	–	124	–	81	–	[53]
Genestet et al.	2020	France	2016–2019	General	–	274	274	0	–	–	M	G & WGS	274	274	21	21	6	7	[54]
Gkaravela et al.	2017	Greece	2009–2011	General	4733	64	–	–	–	–	M	G	69	85	7	7	5	5	[55]
Gupta et al.	2019	India	2014–2017	General	–	103	81	22	103	–	P	PCR	103	103	18	98	5	5	[56]
Ioannidou et al.	2017	Greece	2014–2015	General	–	21	–	–	–	–	P	G	21	21	4	4	3	3	[57]
Jaksuwan et al.	2017	Thailand	2005–2012	R (Any/ Multi)	261	34	–	–	34	–	P	PCR	34	34	34	32	34	28	[16]
Jeon et al.	2018	Korea	2015–2016	General	197		–	–	–	–	P	PCR	74	74	9	3	6	6	[58]
Kidenya et al.	2018	Tanzania	2014–2015	General	–	78	78	0	78	0	–	WGS	–	74	–	3	–	3	[59]
Majumdar et al.	2016	India	–	General	172	70	–	–		–	M	PCR	70	–	9		5		[60]
Merker et al.	2020	Ukraine	2015	R + S (any)	1026	186	–	–	186	0	M	WGS	177	177	85	96	76	78	[61]
Mokry et al.	2019	Slovakia	2009–2017	General	1157	1157	–	–	–	–	P	G	44	44	43	39	17	18	[62]
Molino et al.	2016	Spain	2008–2013	General	4519	2993	–	–	–	–	M	G	2993	–	109	73	13	13	[63]
Munir et al.	2019	India	–	R + S (any)	–	98	–	–	98	_	M	WGS	98	98	34	34	24	24	[64]
Sakhaee et al.	2017	Iran	2013–2016	General	12,725	395	–	–	–	–	P&N	PCR	395	395	25	–	24	–	[65]
Sharma et al.	2017	India	2014–2016	General	2553	483	270	213	_	483	M	G&PCR	483	483	87	–	49	–	[66]
Wondale et al.	2018	Ethiopia	2014–2016	General	1200	161	153	8	135	26	M	G	126	161	3	1	1	3	[67]
Yazisiz et al.	2020	Turkey	2011–2019	General	–	1329	–	–	–	–	M	G	1329	1329	385	312	170	159	[68]
Zhang et al.	2017	China	2014	General	–	325	–	–	325	–	P	–	325	–	32	–	19	–	[69]

Mtb: *Mycobacterium tuberculosis*, TB: tuberculosis, PTB: pulmonary tuberculosis, EPTB: Extra pulmonary tuberculosis, Phen.:Phenotypic, Gen.: Genotypic, INH: Isoniazid, RIF: Rifampicin, P: Lowenstein-Jensen-based Proportion method, M: MGIT 960, N: Nitrate Reductase assay, G: GenoTypeMTBDRplus, PCR: Polymerase chain reaction &Sequencing, WGS: Whole genome sequencing.

[a] The column shows the isolates studied as follow: General (isolates that their antibiotic susceptibility was unknown before study), S (RIF) (isolates that previously reported to be sensitive to rifampicin), R (Any) (isolates that previously reported to be resistant to any anti-TB antibiotics), R (INH) (isolates that previously reported to be resistant to isoniazid), R + S (any) (a collection of isolates with known antibiotic susceptibility (sensitive or resistant) to any anti-TB antibiotics), and R (Any/Multi) (isolates that previously reported to be resistant to any or multi anti-TB antibiotics).

[b] The number of *Mycobacterium tuberculosis* isolates tested for antibiotic sensitivity assay.

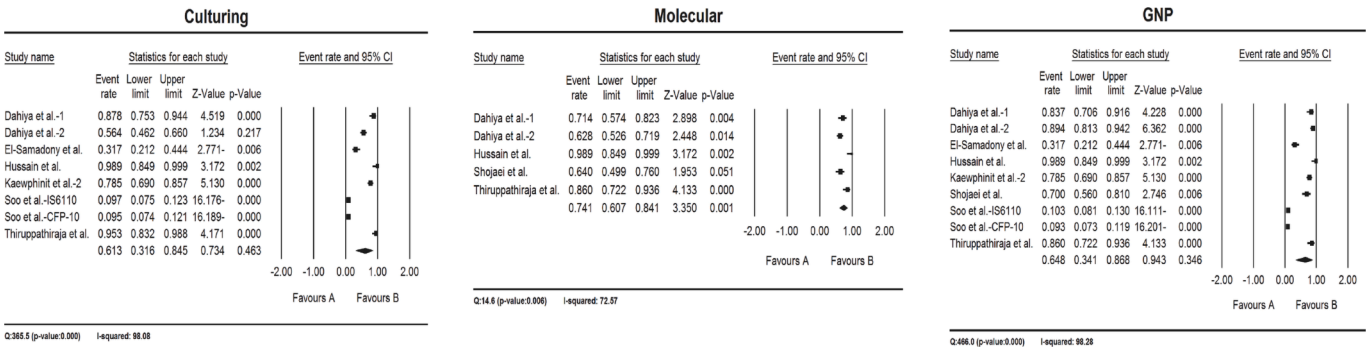

Fig. 2. The forest plot of *M. tuberculosis* resistance to INH and RIF. The plot indicates the rate of resistance to INH and RIF using phenotypic or genotypic methods. The Q-value and I-squared of each analysis are represented below each plot.

or extrapulmonary), number of isolates tested for drug sensitivity, drug sensitivity method, number of isolates resistant to INH and/or RIF, and the number and type of detected gene mutations.

2.4. Statistical analysis

Comprehensive Meta-Analysis software (Version 2.2.064) was used for statistical analyses. The proportion of *M. tuberculosis* resistance to INH and RIF and the prevalence of the most frequent gene mutations were presented by event rate with a 95% confidence interval (CI). The random-effects model was applied for all *meta*-analyses. Subgroup analyses were conducted to measure the source of heterogeneity based on the sampling year, the place (continent), and the method of drug sensitivity assay. The I^2 statistic and Cochrane Q were used to assess the heterogeneity between studies. The quantitative Egger test was applied to measure the possible publication bias. P-values equal to or less than 0.05 were considered as statistically significant.

3. Results

3.1. Search results

In general, 1442 studies were found by database searching. After duplicate publications were removed, 838 studies remained. Following the screening of titles and abstracts, 476 studies remained, and of these, the full texts of 154 studies were evaluated for eligibility. Finally, 29 studies remained for *meta*-analysis. The search strategy flow diagram is shown in Fig. 1. The characteristics of the final studies are shown in Table 1. The status of TB cases (new or retreated) had been only reported in 13 studies (Table 1) in which 86.4 % of the studied cases were new and 13.6% were retreated. The TB type (pulmonary or extrapulmonary) had been reported in 18 studies (Table 1) in which 77.7% of the cases were pulmonary and 22.3% were extrapulmonary.

3.2. M. Tuberculosis antibiotic resistance to INH and RIF

The number of cases resistance to INH or RIF in each study is presented in Table 1. Since the prevalence of *M. tuberculosis* antibiotics resistance can be best studied samples with unknown antibiotic susceptibility, studies with previously known antibiotic susceptibility were not included in prevalence analyses. To this aim, 17 and 13 studies were used to analyze prevalence of resistance to INH or RIF based on phenotypic and genotypic methods, respectively (Fig. 2).

The overall resistance to INH was 17.0% and 17.4% based on phenotypic and genotypic methods, respectively. The overall resistance to RIF was 7.4% and 7.1% based on phenotypic and genotypic methods, respectively (Fig. 2). In each analysis of antibiotic resistance, the Q-value and I^2 test showed significant heterogeneity between the studies (Fig. 2).

3.3 Subgroup analysis of M. Tuberculosis antibiotics resistance to INH and RIF based on the sampling year, the place, and the method of drug sensitivity test

Although in our systematic review only articles published from 2015 to 2020 were included, the sampling year was earlier than 2015 in some studies. Therefore, to perform a subgroup analysis of antibiotic resistance based on the sampling year, the studies were divided into two groups of $\leq$ 2015 and $>$ 2015. Applying these time frames in studies using genotypic drug sensitivity tests, 10 studies were included in the analysis, of which eight and two fell in $\leq$ 2015 and $>$ 2015 categories, respectively. No difference was observed between $\leq$ 2015 and $>$ 2015 studies in terms of resistance to INH or RIF based on genotypic drug sensitivity tests (Table 2). It is important to note that only one study that reported resistance prevalence by phenotypic drug sensitivity tests fell in the $>$ 2015 group, hence statistical analysis was not applicable.

To conduct subgroup analysis of antibiotic resistance based on the placed of conducting the study (continent), the studies were divided into three groups: Africa, Asia, and Europe. No study had been done in other continents. Except for phenotypic method of INH resistance, resistance to both antibiotics with drug sensitivity tests was higher in Asia in comparison to Europe and Africa, although there was no significant heterogeneity between subgroups (Table 3). The frequency of *M. tuberculosis* resistance to INH and RIF in each country is shown in Fig. 3.

To perform subgroup analysis of the resistance of *M. tuberculosis* to INH or RIF based on the method of drug sensitivity tests, the phenotypic methods were divided into two groups (Mycobacteria Growth Indicator Tube 960 (MGIT-960) and Lowenstein-Jensen-based Proportion method), while the genotypic methods were divided into three groups

Table 2
Subgroup analysis of *M. tuberculosis* resistance to INH or RIF based on sampling years.

Antibiotic	Drug sensitivity assay	Sampling year	Studies No.	Resistance (%)	Lower limit	Upper limit	Z-value	p-value	Between group heterogeneity
Isoniazid	**Genotypic**	$\leq$ 2015	8	17.3	6.6	38.4	−2.81	0.005	Q: 0.899 (p-value: 0.343)
		2015 $<$	2	5.9	0.7	37.1	−2.42	0.016	
Rifampicin	**Genotypic**	$\leq$ 2015	8	5.7	2.1	14.9	−5.19	0.000	Q: 0.016 (p-value: 0.898)
		2015 $<$	2	4.9	0.6	31.6	−2.65	0.008	

Table 3
Subgroup analysis of *M. tuberculosis* resistance to INH and RIF based on the continents.

Resistance to INH Group name	Study No.	Prevalence (%)	Lower limit	Upper limit	Z-value	*p*-value	Resistance to RIF Group name	Study No.	Prevalence (%)	Lower limit	Upper limit	Z-value	*p*-value
Phenotypic							**Phenotypic**						
Africa	1	2.4	0.1	41.9	−2.15	0.032	Africa	1	0.8	0.0	27.8	−2.44	0.015
Asia	9	16.0	6.1	35.9	−3.02	0.003	Asia	9	9.7	3.3	25.0	−3.86	0.000
Europe	8	21.1	7.7	46.0	−2.23	0.026	Europe	8	6.6	2.1	19.2	−4.30	0.000
Overall	18	16.6	8.4	30.0	−4.1	0.000	Overall	18	7.4	3.4	15.1	−6.1	0.000
Test of heterogeneity between subgroups: Q: 1.7, p-value: 0.421							**Test of heterogeneity between subgroups**: Q: 1.65, p-value: 0.438						
Genotypic							**Genotypic**						
Africa	2	1.8	0.2	16.2	−3.32	0.001	Africa	2	2.8	0.4	17.2	−3.50	0.000
Asia	6	26.4	9.4	55.3	−1.62	0.105	Asia	6	9.9	3.6	24.5	−3.99	0.000
Europe	6	17.1	5.6	41.6	−2.50	0.013	Europe	6	6.4	2.2	16.9	−4.80	0.000
Overall	14	16.4	7.9	30.9	−3.9	0.000	Overall	14	7.0	3.5	13.3	−7.1	0.000
Test of heterogeneity between subgroups: Q: 4.8, p-value: 0.091							**Test of heterogeneity between subgroups:** Q: 1.43, p-value: 0.49						

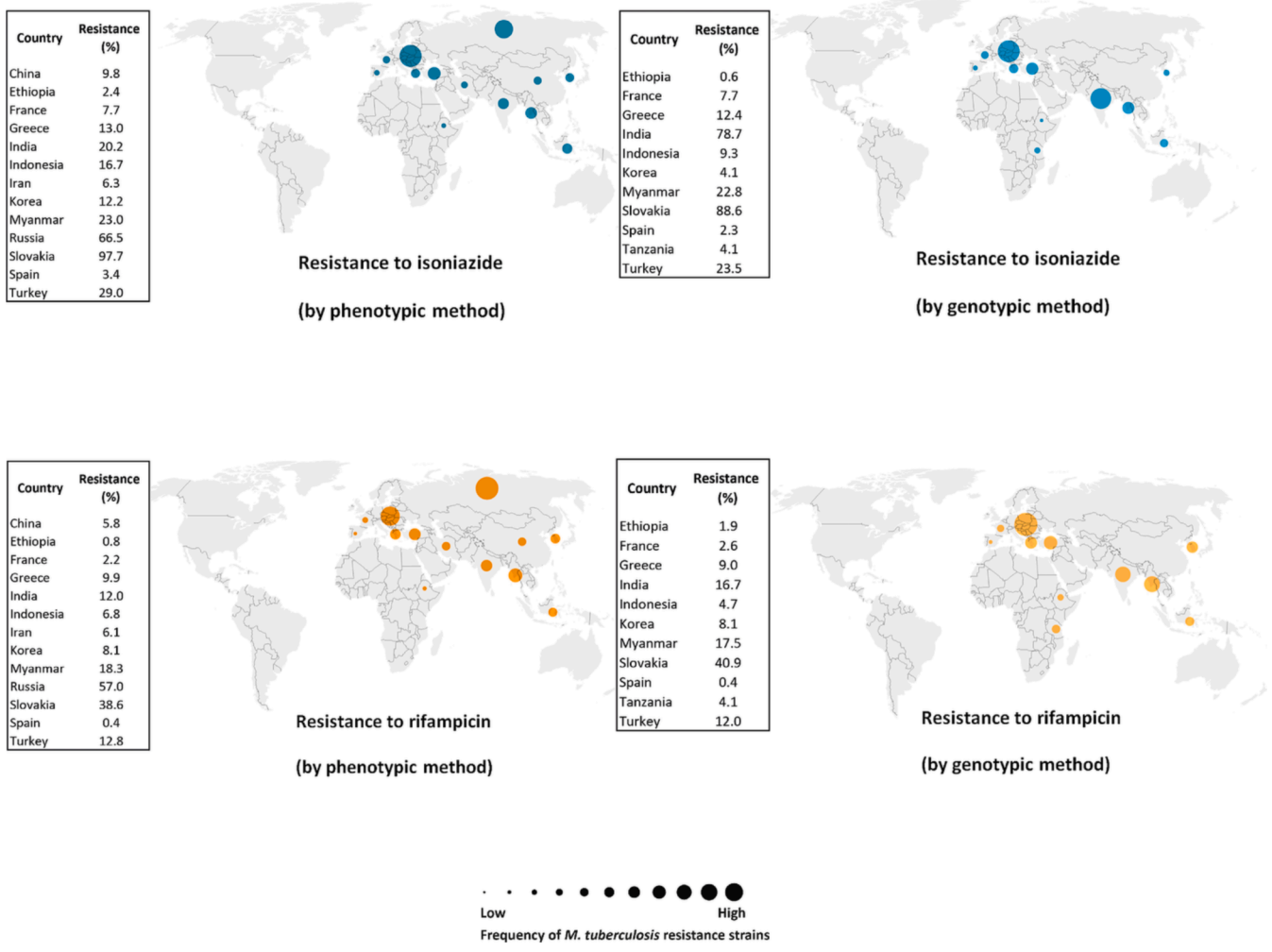

Fig. 3. The frequency of *M. tuberculosis* resistance to INH and RIF in each country. The maps show the frequency of *M. tuberculosis* resistance to INH and RIF in each country. The resistance frequencies (in percentage) are also shown beside each map. The maps were created using Datawrapper (https://www.datawrapper.de/).

Table 4
Subgroup analysis of *M. tuberculosis* resistance to INH and RIF based on the drug sensitivity tests.

Resistance to INH							Resistance to RIF						
Group name	Study No.	Prevalence (%)	Lower limit	Upper limit	Z-value	*p*-value	Group name	Study No.	Prevalence (%)	Lower limit	Upper limit	Z-value	*p*-value
Genotypic							Genotypic						
GenoTypeMTBDRplus	6	13.1	3.1	41.2	−2.42	0.016	GenoTypeMTBDRplus	6	6.1	1.7	20.1	−3.97	0.000
PCR & Sequencing	2	49.1	6.3	93.3	−0.03	0.978	PCR & Sequencing	2	6.3	0.6	41.0	−2.26	0.024
WGS	3	13.6	1.8	57.1	−1.70	0.090	WGS	3	9.2	1.5	40.2	−2.37	0.018
Overall	11	17.6	6.4	39.7	−2.7	0.007	Overall	11	6.9	2.7	16.6	−5.1	0.000
Test of heterogeneity between subgroups: Q: 1.5, p-value: 0.471							**Test of heterogeneity between subgroups**: Q:0.143, p-value: 0.931						
Phenotypic							**Phenotypic**						
MGIT 960	8	11.9	5.4	24.3	−4.55	0.000	MGIT 960	8	5.4	2.1	12.7	−5.94	0.000
Proportion method	8	18.7	8.7	35.7	−3.27	0.001	Proportion method	8	7.5	3.1	17.2	−5.26	0.000
Overall	16	15.0	8.7	24.5	−5.5	0.000	Overall	16	6.4	3.4	11.7	−7.9	0.000
Test of heterogeneity between subgroups: Q: 0.721, p-value: 0.396							**Test of heterogeneity between subgroups**: Q: 0.282, p-value: 0.596						

(GenoTypeMTBDRplus, PCR & sequencing, and whole-genome sequencing). It should be noted that some other methods had been used in only one study, so they were not included in the analysis. A higher rate of resistance to INH and RIF was reported using the Proportion method in comparison to those used MGIT960, although the difference was no statistically significant (Table 4). Regarding genotypic methods, resistance to INH and RIF was higher in studies using PCR & sequencing and whole-genome sequencing, respectively, but again there was no statistically significant heterogeneity between subgroups (Table 4).

3.4. Mutations in common antibiotic resistant genes

Two well-known INH resistant genes (*katG* and *inhA*) and one RIF resistant gene (*rpoB*) along with their most frequent mutations were analyzed. The mutations analyzed for KatG were S315N, S315R, and S315T. The mutations analyzed for InhA were T-8A, T-8C, and C-15 T. The mutations analyzed for RpoB were D516V, D516Y, H526D, H526L, H526Y, and S531L. The number of mutations detected in each study is included in Supplementary Table S1. The result of the analysis of the prevalence of the mutations showed that S315T in KatG (23.7 %), C-15 T in InhA (10.7 %), and S531L in RpoB (13.5 %) were the most prevalent mutations. There was significant heterogeneity between mutation groups (Table 5).

3.5. Publication bias

To analyze publication bias, the prevalence of resistance to INH and RIF (using both phenotypic and genotypic methods) was applied. The possible publication bias was checked by Egger's linear regression test. In all analyses the p-value for Egger's linear regression test was higher than 0.05, indicating no publication bias.

4. Discussion

The most effective strategies to control TB include early and accurate diagnosis as well as treatment with appropriate antibiotics [21]. Identifying the prevalence of MDR strains of *M. tuberculosis* assists in the control and planning of treatments [13]. The most effective drugs for TB treatment are INH, RIF, Ethambutol, and Pyrazinamine. However, achieving appropriate treatment outcomes with these drugs may not be successful given the emergence of drug-resistant strains. Drug resistance is a major cause of treatment failure in TB, especially when the strains become resistant to the primary drugs such as INH and RIF, which lead to the development of MDR-TB [17,22,23]. Generally, resistance to INH is more prevalent than that to RIF. Furthermore, about 90% of RIF-resistant strains are also resistant to INH [24]. According to our *meta*-analysis, the overall resistance to INH and RIF was about 17.2 % (17.0 % by phenotypic and 17.4% by genotypic methods) and 7.3 % (7.4 % by phenotypic and 7.1 % by genotypic methods), respectively. These percentages are consistent with those reported by other studies [25–27]. It is noteworthy that in our study, there was significant heterogeneity between the studies, indicating that in different parts of the world, the prevalence of INH and RIF resistant TB cases are significantly different. This difference may reflect the quality of studies, the efficiency of detection methods, or the true difference in bacterial resistance patterns in different geographical places. Also, the studies included in this *meta*-analysis focused on clinical cases of *M. tuberculosis* isolated from TB-suspected/confirmed patients and not from general population. Therefore, the antibiotics prevalence obtained in the study could not be attributed to the general population, and more studies are required to find the *M. tuberculosis* antibiotic resistance patterns in different populations.

In our *meta*-analysis, the resistance to INH and RIF was more prevalent in Asia compared to other continents. This result is consistent with previous reports in which the highest rate of *M. tuberculosis* drug

Table 5
Prevalence of mutations in protein associated to isoniazid (INH) and rifampicin (RIF) resistance of *M. tuberculosis*.

INH resistance associated protein Mutation	Study No.	Prevalence (%)	Lower limit	Upper limit	Z-value	*p*-value
InhA						
C-15 T	8	10.7	5.0	21.4	−5.08	0.000
T-8A	3	0.3	0.1	1.5	−7.33	0.000
T-8C	2	0.5	0.1	3.1	−5.52	0.000
Overall	13	3.8	2.0	7.2	−9.4	0.000
Test of heterogeneity between subgroups: Q: 22.2, p-value: 0.000						
KatG						
S315N	2	0.3	0.0	2.0	−5.74	0.000
S315R	2	0.3	0.0	2.5	−5.52	0.000
S315T	13	23.7	14.4	36.5	−3.73	0.000
Overall	17	13.2	7.9	21.0	−6.6	0.000
Test of heterogeneity between subgroups: Q: 34.3, p-value: 0.000						

RIF resistance associated protein Mutation	Study No.	Prevalence (%)	Lower limit	Upper limit	Z-value	*p*-value
RpoB						
D516V	8	2.3	1.1	4.7	−9.67	0.000
D516Y	4	3.6	1.3	9.6	−6.14	0.000
H526D	5	1.1	0.4	2.9	−8.84	0.000
H526L	4	2.0	0.6	6.8	−6.07	0.000
H526Y	8	1.8	0.8	3.9	−9.95	0.000
S531L	12	13.5	8.0	21.9	−6.22	0.000
Overall	41	3.9	2.8	5.3	−18.7	0.000
Test of heterogeneity between subgroups: Q: 34.2, p-value: 0.000						

resistance had been observed in Asia and Africa [1]. It should be pointed out that only one or two studies from Africa were included in our *meta*-analysis, which undermines the importance of the analysis outcome and suggests performing more studies on this topic. By contrast, more studies from Asia and Europe were included in this review, making statistical comparisons more accurate, which showed that resistance to INH and RIF is more prevalent in Asia than Europe. This difference may be due to the lower level of health programs, immigration issues, previous TB treatments, etc. in Asia [28,29], and these data are concordant with the WHO's global TB report, because of target treatment success in European high TB burden countries reached or exceeded a 90% rate [1].

Generally, detection of *M. tuberculosis* resistance is performed by phenotypic and/or genotypic approaches. The most frequently-used phenotypic approaches include culture-based test, Proportion method [30], MGIT960 system [31], and resazurin microtiter assay[1] (REMA) plate method [32,33]. The phenotypic approaches are relatively difficult to perform and involve time-consuming protocols which may last from weeks to months. As a result, advances in *M. tuberculosis* molecular biology and its completely sequenced genome [34] led to the development of novel genotypic approaches for rapid detection of *M. tuberculosis* drug resistance detection [2]. The well-known genotypic approaches for this purpose include the GenoTypeMTBDRplus system, polymerase chain reaction (PCR), partial sequencing, and whole-genome sequencing.

The results of our subgroup analysis based on the method of drug susceptibility tests showed that there was no significant difference between the frequency of INH and RIF resistance using different phenotypic or genotypic methods. The only exception was related to detection of INH resistance using genotypic methods, in which the rate of resistance detected using PCR & sequencing method was higher in comparison to more novel and more accurate methods of GenoTypeMTBDRplus and whole-genome sequencing. The assessment of the accuracy of each method was out of the scope of the present study, but it could be stated that genotypic methods are novel, faster, and seem to be more accurate [35], particularly, if a wider range of genes and mutation are explored.

Finding a trend in antibiotic resistance over years will help health officials and researchers to come up with a better and more effective way to control pathogens. Here, due to the vast range of sampling years in some studies, the best way to assay the effect of sampling years was by dividing them into studies done before and after 2015. Of course, the results showed no difference in the prevalence of resistance to INH and RIF before and after 2015. However, using our inclusion criteria only two studies fell in the $>$ 2015 group, so more studies are needed to provide a more accurate account of any changes in INH and RIF resistance over years.

TB drug resistance is mainly associated with different gene mutations. Mutation in *katG* gene is the most common cause of creating INH resistance strains [36], but other genes such as *inhA* also play important roles in this regard. Catalase peroxidase, which converts INH to a physiologically active form, is encoded by the *katG* gene [37]. The *inhA* regulatory region encodes nicotinamide adenine dinucleotide-dependent enoyl-acyl carrier protein reductase, the primary target of active INH as well as Ethionamide and Prothionamide [38]. Rifampicin resistance is usually induced by mutations in *rpoB* gene, which encodes the β-subunit of the RNA polymerase [39]. Our *meta*-analysis showed that S315T in KatG and C-15 T in InhA are the most prevalent mutations causing resistance to INH, while S531L in RpoB is the most important mutation causing resistance to RIF. This result is in agreement with the results of other studies who showing that S315T and C-15 T in KatG and InhA proteins were the most common causes of resistance to INH, and S531L and lower levels of H526Y were the most common causes of resistance to RIF [14,15,18,19,40,41]. Further research is needed to establish which changes are important in the pandemic of drug-resistant *M. tuberculosis*, particularly MDR-TB. This will help to guide both local TB control and national MDR-TB policies [42].

Despite its strengths, our study had a number of limitations. First, studies published before 2015 were not included, so the trend of resistance to INH and/or RIF could not be accurately determined. Second, only two antibiotics (INH and RIF) were investigated, hence the prevalence of resistance to other important antibiotics such as Ethambutol, and Pyrazinamide was missed. Finally, a small number of most-known mutations were studied, which may cause missing important

mutations associated with INH and RIF resistance.

5. Conclusions

We recommend future studied to involve longer time ranges as well as more antibiotics and more resistance-associated mutations. Altogether, here we showed that the prevalence of INH and RIF resistance was heterogenic in different parts of the world, which may be associated with the success rate of TB control strategies and plans. We also showed that due to S531L, S315T, and C-15 T mutations, INH and RIF-resistant *M. tuberculosis* isolates were widely distributed. Thus, it would be diagnostically and epidemiologically beneficial to track these gene mutations among resistant isolates.

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Ethical Statement

This study was approved by deputy of research and technology of Kermanshah University of Medical Sciences (ethic number: IR.KUMS.REC.1399.856).

CRediT authorship contribution statement

Mosayeb Rostamian: Data curation, Visualization, Writing – review & editing. **Sara Kooti:** Data curation, Visualization, Writing – original draft, Writing – review & editing. **Ramin Abiri:** Conceptualization, Investigation, Project administration, Writing – review & editing. **Saeed Khazayel:** Visualization, Software. **Sepide Kadivarian:** Data curation. **Soroush Borji:** Data curation. **Amirhooshang Alvandi:** Supervision, Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2023.100379.

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