Beijing genotype of *Mycobacterium tuberculosis* is associated with extensively drug-resistant tuberculosis: A global analysis

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Abstract

We found that the frequency of Beijing genotype among XDR-TB strains was high. The data in this study would help guide the TB control program, and we however need further investigation to confirm the reliability of the present findings.

Keywords: *Mycobacterium tuberculosis*, Tuberculosis, Beijing, MIRU-VNTR, IS6110-RF
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Dear Editor;

Tuberculosis is one of the most important infectious diseases in human history that is also known as the white plague. Tuberculosis is caused by the infection with *Mycobacterium tuberculosis* and is the second leading cause of death after HIV among the infectious aspects [1,2]. According to the WHO, there were about 10 million people who fell ill with TB in 2019; Furthermore, there were 1.5 million TB deaths in 2019 [3]. Despite more than a century of extensive studies, the control and eradication of tuberculosis have yet remained a global challenge and one of the medical emergencies considered by the World Health Organization [4,5].

It is not possible to eradicate *Mtb* due to the infection of a quarter of the world's population with latent TB. In addition, other factors such as co-infection with infectious agents (HIV, HTLV-1, HCV, and HBV), lack of effective vaccine in adults, and increased MDR and XDR strains all contribute to failure in the complete eradication of TB. However, continuous monitoring of patient data and genetic characterizations of *Mtb* strains in different geographical areas can be helpful in setting local programs and global policies to control and reduce TB disease [6–8].

Molecular typing of *Mtb* strains is an important tool in evaluating the transmission and outbreaks of this disease performed using molecular techniques, including *IS6110*-RFLP, Spoligotyping, and the variable number of tandem repetition of mycobacterial interspersed repetitive units typing (MIRU-VNTR) [9]. Nowadays, nine superfamilies have been identified for *M. tuberculosis* complex, including *Mycobacterium africanum*, *Mycobacterium bovis*, Beijing, EAI, CAS, T, Haarlem, X, and LAM, which account for more than a quarter of TB cases due to infection with the Beijing family [10]. Interestingly, most reported MDR-outbreaks are caused by the Beijing family [11]. Recently, we showed in a comprehensive literature review that the Beijing family is the most dominant resistant genotype in Iran; We also found that the frequency of the Beijing family among Iranian drug-resistance strains is significantly higher than the other genotypes [12]. However, the diversity of XDR-TB genotypes has not yet been properly elucidated. This study aimed to evaluate the frequency of common genotypes among the XDR-TB strains worldwide.

To collect the studies relevant to the genotyping XDR-TB strains of computer-assisted literature indicates search in PubMed, Scopus, and Google Scholar databases using the search terms based on MesH such as 'Tuberculosis', '*Mycobacterium tuberculosis*', '*M. tuberculosis,*' 'Extensively drug-resistant TB', 'Genotyping'', '*IS6110*-RFLP', 'Spoligotyping', and 'MIRU-VNTR'. Relevant studies were collected without restriction on publication dates; Also, the bibliography section of the articles was carefully examined in order not to miss the potential articles. We considered studies published in English with their available full-texts and considered XDR-TB genotypes as eligible studies using standard methods, including *IS6110*-RFLP, Spoligotyping, MIRU-VNTR, or whole-genome sequencing, and excluded articles on non-XDR-TB subjects, studies with repetitive samples, studies with unclear results and insufficient data, and studies published in non-English languages. Processing the literature search and evaluation of eligible studies was performed by two independent authors (MK and MM). The required data such as first author, publication year,

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TABLE 1. Characteristics of included studies

First author	Publication year	Country	Region	MTB strains	XDR strains	MTB genotypes distribution								Typing method	Ref
						Beijing		CAS/Delhi		Haarlem		East African-Indian			
						XDR	Total	XDR	Total	XDR	Total	XDR	Total		
Ghebremichael	2008	Sweden	Europe	400	1	1	48	0	31	0	36	0	36	Spoligotyping IS6110	[13]
Perdigão	2010	Portugal	Europe	NA	26	0	0	0	0	0	0	0	0	MIRU-VNTR	[14]
Kozinska	2011	Poland	Europe	297	19	2	NA	0	NA	0	NA	0	NA	Spoligotyping MIRU-VNTR	[15]
Mokrousov	2015	Republic of Karelia	Europe	78	6	5	43	0	0	0	4	0	0	Spoligotyping MIRU-VNTR	[16]
Roycroft	2018	Ireland	Europe	42	3	2	14	0	3	0	2	0	2	MIRU-VNTR	[17]
Sinkov	2018	former Soviet Union	Europe	149	7	0	0	0	0	0	0	0	0	Spoligotyping	[18]
Pole	2020	Latvia	Europe	411	69	38	104	0	0	0	27	0	0	Spoligotyping MIRU-VNTR IS6110	[19]
Ca'ceres	2014	Peru	America	227	142	13	NA	0	NA	62	NA	0	NA	Spoligotyping	[20]
Juarez-Eusebio	2017	Mexico	America	54	1	0	3	0	0	0	5	0	2	MIRU-VNTR	[21]
Nieto Ramirez	2020	Colombia	America	311	4	4	37	NA	NA	NA	NA	NA	NA	MIRU-VNTR	[22]
Masjedi	2006	Iran	Asia	2030	12	0	NA	0	NA	8	NA	4	NA	Spoligotyping IS6110	[23]
Setareh	2009	Belarus	Asia	138	30	15	NA	NA	NA	NA	NA	NA	NA	RFLP	[24]
Lai	2010	Taiwan	Asia	39	9	4	21	0	0	NA	5	0	0	Spoligotyping MIRU-VNTR	[25]
Hasan	2010	Pakistan	Asia	9523	113	5	NA	33	NA	0	NA	1	NA	Spoligotyping MIRU-VNTR IS6110	[26]
Ajbani	2011	India	Asia	3899	150	94	NA	21	NA	1	NA	13	NA	Spoligotyping	[27]
Surcouf	2011	Cambodia	Asia	101	1	0	57	0	0	0	0	1	15	Spoligotyping	[28]
Vadwai	2011	India	Asia	5	3	3	4	0	0	0	0	0	0	Spoligotyping MIRU-VNTR	[29]
Zhang	2012	China	Asia	55	2	2	47	0	NA	0	NA	0	NA	MIRU-VNTR	[30]
Arjomandzadegan	2012	Belarus and Iran	Asia	202	31	15	98	NA	NA	NA	NA	NA	NA	Spoligotyping	[31]
Yuan	2013	China	Asia	804	13	12	0	0	0	0	0	0	0	MIRU-VNTR	[32]
Poudel	2013	Nepal	Asia	109	13	9	NA	1	NA	0	0	0	0	Spoligotyping MIRU-VNTR	[33]
Arora	2013	India	Asia	311	50	21	NA	10	NA	0	NA	2	NA	Spoligotyping	[34]
Zhang	2014	China	Asia	158	10	6	102	NA	NA	NA	NA	NA	NA	Spoligotyping	[35]
Hu	2015	China	Asia	1332	15	15	997	0	30	0	0	0	0	Spoligotyping MIRU-VNTR	[36]
Disratthakit	2015	Thailand	Asia	192	28	16	143	0	0	0	0	0	18	Spoligotyping MIRU-VNTR	[37]
Zhao	2015	China	Asia	116	58	44	NA	0	NA	0	NA	0	NA	Spoligotyping IS6110	[38]
Hu	2015	China	Asia	166	5	2	138	NA	5	0	0	0	0	Spoligotyping MIRU-VNTR	[39]
Rufai	2016	India	Asia	234	15	7	NA	3	NA	1	NA	1	NA	Spoligotyping MIRU-VNTR	[40]
Khanipour	2016	Iran	Asia	23	4	2	9	0	1	2	10	0	0	Spoligotyping MIRU-VNTR	[41]
Hu	2016	China	Asia	1222	6	5	967	0	0	0	0	0	8	Spoligotyping MIRU-VNTR	[42]
Singhal	2016	India	Asia	219	10	6	NA	4	NA	0	NA	0	NA	MIRU-VNTR	[43]
San	2018	Myanmar	Asia	256	8	NA	210	NA	3	NA	1	NA	28	Spoligotyping MIRU-VNTR	[44]
Kazemian	2019	Iran	Asia	33	1	1	13	0	4	0	0	0	1	RFLP-PGRS	[45]
Andrews	2008	Tugela Ferry, KwaZulu-Natal	Africa	17	12	0	0	0	0	0	0	0	0	Spoligotyping IS6110	[46]
Said	2012	Mpumalanga, Gauteng, Limpopo	Africa	336	24	6	69	0	0	0	0	9	78	Spoligotyping MIRU-VNTR	[47]
Klopper	2013	Eastern Cape	Africa	334	108	103	236	0	0	0	0	0	0	Spoligotyping IS6110	[48]
Gandhi	2013	KwaZulu-Natal	Africa	NA	86	0	0	0	0	0	0	0	0	IS6110	[49]
Gandhi	2014	KwaZulu-Natal	Africa	286	92	0	33	0	3	0	8	0	2	Spoligotyping	[50]
Cohen	2015	KwaZulu-Natal	Africa	340	67	6	81	0	7	0	0	1	9	Spoligotyping IS6110	[51]
Dookie	2016	KwaZulu-Natal	Africa	60	28	0	NA	0	0	0	0	0	0	IS6110	[52]
Kateete	2019	Swatini, Somalia and Uganda	Africa	38	12	3	8	1	1	0	0	0	1	MIRU-VNTR	[53]

country, geographic region, frequency of *Mtb* strains, frequency of XDR-TB strains, distribution of *Mtb* genotypes, typing method, and references are summarized in Table 1.

The frequency of each XDR-TB genotype was reported using event rate corresponding confidence intervals (95% CIs); Moreover, the odds ratio with 95% CIs was used to measure the relationship between XDR-TB and each of the genotypes. Heterogeneity was measured using the I^2 index and Cochrane *Q*-test. Egger's *p*-value and Begg's *p*-value were used to evaluating the publication bias. All the statistical analyses were performed using the Comprehensive Meta-Analysis software (Biostat, Englewood, NJ).

After evaluating the potential documents, 41 eligible studies were identified [13–53]. These studies were conducted between 2006–2020 in Europe, Latin America, Asia, and Africa. In these studies, genotyping of *Mtb* strains was performed using *IS6110*-RFLP, Spoligotyping, and MIRU-VNTR methods. The data of 24,659 Mtb strains were evaluated in this study.

The frequency of XDR-TB strains was estimated to be about 8.3% (95% CI: 5.1–13.1; I^2: 98.2; *Q*-value: 2120.6; Egger's *p*-value: 0.84; Begg's *p*-value: 0.08); Furthermore, according to the subgrouping analysis, the prevalence of XDR-TB in Africa, Latin America, Asia, and Europe was estimated to be 29.6% (95% CI: 19.4–42.2; I^2: 93.7; *Q*-value: 96.4; Egger's *p*-value: 0.77; Begg's *p*-value: 0.76), 7.3% (95% CI: 2–7.8; I^2: 98.0; *Q*-value: 103.1; Egger's *p*-value: 0.29; Begg's *p*-value: 0.50), 5.8% (95% I: 3.3–10.2; I^2: 97.5; *Q*-value: 915.2; Egger's *p*-value: 0.2; Begg's *p*-value: 0.39), and 5.9% (95% CI: 2.8–12.1; I^2: 88.1; *Q*-value: 42.1; Egger's *p*-value: 0.02; Begg's *p*-value: 0.3), respectively.

Beijing and Haarlem genotypes were the most prevalent and the least common genotypes among the XDR-TB strains, respectively, so that global distribution of Beijing, Dehli-Cas, EAI, and Haarlem genotypes were 40.9% (95% CI: 29.1–53.8; I^2: 88; *Q*-value: 300.8; Egger's *p*-value: 0.35; Begg's *p*-value: 0.42), 6% (95% CI: 3.6–9.9; I^2: 62.4; *Q*-value: 82.5; Egger's *p*-value: 0.01; Begg's *p*-value: 0.01), 4.7% (95% CI: 2.8–8; I^2: 53.7; *Q*-value: 71.4; Egger's *p*-value: 0.02; Begg's *p*-value: 0.01), and 4% (95% CI: 1.8–8.8; I^2: 79.6; *Q*-value: 152.2; Egger's *p*-value: 0.01; Begg's *p*-value: 0.01), respectively. Based on the results of subgrouping analysis, the frequency of XDR-TB strains belonging to Beijing family among Asians, Europeans, Africans and Latin Americans, respectively, was 54.5% (95% CI: 42.3–66.3; I^2: 77.8; *Q*-value: 90.3; Egger's *p*-value: 0.9; Begg's *p*-value: 0.4), 29.5% (95% CI: 8.7–64.8; I^2: 77.6; *Q*-value: 22.4; Egger's *p*-value: 0.1; Begg's *p*-value: 0.45), 10.3% (95% CI: 1.6–44.9; I^2: 93.6; *Q*-value: 110.0; Egger's *p*-value: 0.1; Begg's *p*-value: 0.9), and 35.1% (95% CI: 1.5–95.2; I^2: 90.1; *Q*-value: 10.1).

According to the results of subgrouping analysis, the frequency of XDR-TB strains belonging to the Beijing family among Asians, Europeans, Africans and Latin Americans, respectively, was 54.5% (95% CI: 42.3–66.3; I^2: 77.8; *Q*-value: 90.3; Egger's *p*-value: 0.9; Begg's *p*-value: 0.4), 29.5% (95% CI: 8.7–64.8; I^2: 77.6; *Q*-value: 22.4; Egger's *p*-value: 0.1; Begg's *p*-value: 0.45), 10.3% (95% CI: 1.6–44.9; I^2: 93.6; *Q*-value: 110.0; Egger's *p*-value: 0.1; Begg's *p*-value: 0.9), and 35.1% (95% CI: 1.5–95.2; I^2: 90.1; *Q*-value: 10.1), respectively.

We observed a significant relationship between the Beijing genotype and XDR-TB but there was no significant relationship between other genotypes and XDR-TB (OR: 2.48; 95% CI: 1.84–3.34; *p*-value: 0.01; I^2: 85.5; *Q*-value: 193.9; Egger's *p*-value: 0.05; Begg's *p*-value: 0.34). In the subgrouping analysis, there was a significant relationship between Beijing genotype and XDR-TB among the Asian population (OR: 7.68; 95% CI: 3.17–18.58; *p*-value: 0.01; Egger's *p*-value: 0.37; Begg's *p*-value: 0.59), among the Africans (OR: 12.93; 95% CI: 0.45–366.7; *p*-value: 0.01; Egger's *p*-value: 0.13; Begg's *p*-value: 0.3), and among the Europeans (OR: 2.29; 95% CI: 0.68–4.43; *p*-value: 0.01; Egger's *p*-value: 0.19; Begg's *p*-value: 0.30). However, no significant correlation was observed in the Latin American population (OR: 0.24; 95%CI: 0.14–0.42; *p*-value: 0.01). Therefore, the frequency of Beijing genotype among the XDR-TB strains was significantly higher than Dehli-Cas, EAI, and Haarlem genotypes. Based on the available data, identification of the Beijing genotypes, especially in the patients with treatment failure, is a reliable index for the XDR-TB cases.

The Beijing genotype *Mycobacterium tuberculosis* was first introduced by Van Soolingen et al., in 1995 from Beijing (China), and after a while, several outbreaks of Beijing genotype were reported and identified in Asia, South Africa, Germany, Canary Islands, Russia, Thailand and the United States [54,55]. According to the available reports, more than a quarter of tuberculosis cases belong to the Beijing genotype [56]. Beijing strains have several remarkable properties: (1) they are mostly associated with active TB, (2) they are associated with treatment failure and multiple drug resistance, (3) they are capable of efficient proliferation in the lung macrophages and spread in the population, and (4) they are genetically unstable. In particular, mutt gene alleles cause drug resistance and alter bacterial morphology [57–59]. Numerous pieces of evidence have been reported regarding the relationship between the Beijing genotype and MDR-TB so that this genotype can be considered as a biomarker for drug-resistant TB [60–62]. We showed for the first time in a comprehensive analysis that the Beijing family is the most predominant genotype among the XDR-TB strains. Based on the present results, the Beijing genotype can lead to the occurrence of several serious outbreaks in close geographical areas, and therefore, the identification and screening of these patients from an epidemiological point of view is an important strategy in the TB control program. However, our study had several limitations: (1) the sample size was small, (2) heterogeneity was significant, and (3) in some cases, publication bias was significant. We found that the frequency of Beijing genotype among XDR-TB strains was high. The data in this study would help guide the TB control program, and we however need further investigation to confirm the reliability of the present findings.

Transparency declaration

The authors have no conflict of interest.

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