

• 实验技术及其应用 •

四川省甘孜州 2018—2025 年结核分枝杆菌临床分离株耐药及基因突变情况分析

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摘要:目的 分析 2018 年 9 月至 2025 年 8 月四川省甘孜州 793 例结核分枝杆菌临床分离株对利福平和异烟肼的耐药情况及突变位点情况, 以便为当地结核病防治工作提供科学依据。方法 采用 DNA 微阵列芯片(基因芯片)法对收集得到的结核分枝杆菌进行利福平和异烟肼耐药基因快速分子检测, 分析该地区耐药情况和耐药基因突变情况, 并使用卡方分析比较不同性别、年龄和不同农业景观区域的耐药情况。结果 793 例结核分枝杆菌对利福平和异烟肼的总体耐药率为 18.16%, 利福平耐药率为 12.99%, 异烟肼耐药率为 10.7%, 耐多药率为 5.55%。不同性别患者耐药率无统计学差异。0 ~ <20 岁患者总体耐药率(21.67%)、异烟肼耐药率(14.28%)、耐多药率(6.90%) 最高, 40 ~ <60 岁组利福平耐药率(14.56%) 最高, 不同年龄组总体耐药、利福平耐药、异烟肼耐药、耐多药间差异均无统计学意义。半农半牧地区耐药率高于纯农区和纯牧区, 但总体耐药与利福平耐药间差异均无统计学意义, 而异烟肼耐药与耐多药间差异具有统计学意义($\chi^2=9.089, 13.680, P<0.05$)。利福平耐药基因突变以 *rpoB531*(C→T) 最高, 占 33.01%, 其次为 516(G→T), 占 25.24%, 再次为 511(T→C), 占 18.45%, 异烟肼耐药以 *katG* 耐药基因突变为主, 占 92.94%, 其中 *katG315*(G→C) 为 84.71%, *katG315*(G→A) 为 8.24%, *inhA* 耐药基因突变占 8.24%。耐多药以 *rpoB*(516(G→T)) *katG*(315(G→C)) 突变为主, 占 52.27%。结论 甘孜州结核病利福平、异烟肼耐药严重, 0 ~ <20 岁低年龄组较其他年龄组耐药更严重, 半农半牧地区较纯农区和纯牧区耐药更严重, 利福平与异烟肼耐药基因突变以高水平耐药位点突变为主。该地区需加强结核病耐药检测和发现, 加强患者规范化治疗与管理, 减少耐药结核病的产生和传播, 特别应注意低年龄人群和半农半牧区人群的结核病耐药防控。

关键词: 结核分枝杆菌; 微阵列基因芯片; 耐多药结核; 利福平耐药; 异烟肼耐药

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Analysis of drug resistance and gene mutations in clinical *Mycobacterium tuberculosis* isolates, Ganzi Prefecture, Sichuan, 2018 – 2025

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Abstract: **Objective** To analyse the rifampicin and isoniazid resistance patterns and mutation sites in 793 clinical isolates of *Mycobacterium tuberculosis* from Garze Tibetan Autonomous Prefecture, Sichuan Province, collected between September 2018 and August 2025, so as to provide scientific basis for local tuberculosis prevention and control. **Methods** DNA microarray gene chips were used to perform rapid molecular detection of rifampicin and isoniazid resistance genes in collected *M. tuberculosis* isolates. The drug resistance and mutation of resistance genes in the region were analyzed, and chi square analysis was used to compare the drug resistance of different genders, ages, and agricultural landscape areas. **Results** The overall resistance rate of 793 cases of *Mycobacterium tuberculosis* to rifampicin and isoniazid was 18.16%, with a rifampicin resistance rate of 12.99%, isoniazid resistance rate of 10.7%, and multidrug resistance rate of 5.55%. According to statistical analysis, there was no significant difference in drug resistance rates between patients of different genders. The overall drug resistance rate (21.67%), isoniazid resistance rate (14.28%), and multidrug resistance rate (6.90%) were highest in patients aged 0 – <20, and the rifampicin resistance rate (14.56%) was highest in the 40 – <60 age group. Differences in overall resistance,

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rifampicin resistance, isoniazid resistance and multidrug resistance between age groups were not statistically significant. Drug resistance rates were higher in semi-agricultural/semi-pastoral areas than in purely agricultural or pastoral areas. However, no statistically significant differences were observed between overall drug resistance and rifampicin resistance. A statistically significant difference was found between isoniazid resistance and multidrug resistance ($\chi^2 = 9.089, 13.680, P < 0.05$). The predominant rifampicin resistance mutation site was *rpoB*531 (C → T) (33.01%), followed by 516 (G → T) (25.24%) and 511 (T → C) (18.45%). Isoniazid resistance was predominantly mediated by *katG* gene mutations (92.94%), comprising *katG*315 (G → C) (84.71%) and *katG*315 (G → A) (8.24%), while *inhA* gene mutations accounted for 8.24%. Multidrug resistance was predominantly mediated by *rpoB*(516(G → T) *katG*(315(G → C) mutations, accounting for 52.27%. **Conclusion** Rifampicin and isoniazid resistance in tuberculosis cases from Garze Tibetan Autonomous Prefecture is severe. Resistance is more pronounced in the 0 - <20 age group compared to other age cohorts, and is more prevalent in semi-agricultural/semi-pastoral areas than in purely agricultural or pastoral regions. Resistance mutations predominantly involve high-level resistance sites for both rifampicin and isoniazid. The region requires enhanced tuberculosis drug resistance testing and detection, strengthened standardised treatment and management of patients, and reduced generation and transmission of drug-resistant tuberculosis, and pay special attention to tuberculosis drug resistance prevention and control among low-age groups and people living in semi-agricultural and semi-pastoral areas.

Keywords: *Mycobacterium tuberculosis*; Microarray gene chip; Multidrug-resistant tuberculosis (MDR-TB); Rifampicin resistance; Isoniazid resistance

结核病是由结核分枝杆菌 (*Mycobacterium tuberculosis*, MTB) 感染引发的慢性传染性疾病, 至今仍是全球范围内导致死亡的主要单一传染病之一。根据世界卫生组织 (WHO)《2025 年全球结核病报告》^[1], 2024 年全球新发结核病患者约 1 070 万例, 其中耐多药/利福平耐药结核病患者为 39 万例 (3.6%), 同期因结核病死亡的病例数达 123 万例。我国结核病 2024 年新发患者数为 69.6 万, 估算发病率为 49/10 万, 死亡数为 2.5 万, 死亡率 1.9/10 万, 新发耐多药/利福平耐药结核病 (MDR/RR-TB) 患者为 2.8 万, 占全球 7.1%, 此类患者治疗周期更长、医疗费用更高、治愈率更低、病死率更高, 且易造成耐药菌株传播, 加重医疗负担, 严重危害公共卫生安全^[1]。四川省地处我国西部, 是我国结核病高负担地区之一^[2,3], 甘孜藏族自治州地处四川省西部, 属大陆性高原山地气候, 产业以高原农牧业为主, 有农区、牧区、半农半牧地区^[4-6], 因高海拔、天气严寒、游牧人口占比高、医疗资源分布不均等特点, 结核病疫情重, 2020 年报告发病率 217.01/10 万, 患者诊断延迟重, 且治疗依从性较差^[7-8], 结核病是甘孜藏区重大公共卫生挑战。

为了解甘孜藏族自治州结核病患者常用一线抗结核药物利福平、异烟肼的耐药情况, 及耐药基因突变情况, 考虑到结核病传统药敏检测周期长且操作繁琐, 而 DNA 微阵列芯片 (基因芯片) 结核分枝杆菌分子耐药检测方法可同时进行重要一线抗结核药物利福平 (*rpoB*) 与异烟肼 (*katG*、*inhA*) 耐药基因检测, 灵敏度和特异度高, 操作简单, 可在一天内报告结果^[9-10], 本研究采用该检测方法, 对甘孜州 18 县 (市) 人民医院培养获得并送至甘孜州疾病预防控制中心

中心的结核分枝杆菌临床分离株进行利福平 (*rpoB*) 与异烟肼 (*katG*、*inhA*) 耐药基因检测, 共分析了从 2018 年 9 月至 2025 年 8 月分离的 793 例结核分枝杆菌临床样本, 以便为甘孜州结核病患者抗结核治疗方案选择和当地结核病防控工作提供科学依据。

1 材料与方法

1.1 研究对象与菌株来源 2018 年 9 月至 2025 年 8 月, 对四川省甘孜藏族自治州 18 个县 (市) 结核病定点医疗机构诊断的结核病患者进行痰样本采集、酸性改良罗氏培养基分离培养和基因芯片法鉴定, 得到 872 株结核分枝杆菌临床分离株, 有 79 株菌株因患者基本信息不全和样本异常无法获得基因芯片结果排除, 最终纳入 793 名研究对象。

1.2 研究内容和方法

1.2.1 仪器与试剂 仪器包括北京博奥 Extractor TM36 核酸提取仪、BioMixer TMII 四梯度杂交仪 (46℃/48℃/50℃/52℃)、LuxScan TM10K-B 双通道激光扫描仪、Thermo Scientific StepOnePlus 实时荧光定量 PCR 仪。实验试剂为北京博奥晶芯结核分枝杆菌耐药基因检测试剂盒 (用于 DNA 微阵列芯片法) 与珠海贝索改良罗氏培养基。

1.2.2 DNA 微阵列芯片结核分枝杆菌耐药检测 使用磁珠法从收到的临床分离纯培养物提取结核分枝杆菌 DNA, 加入 16S rRNA 内参基因, 核酸纯度要求 A260/A280 = 1.8 ~ 2.0。DNA 经过 PCR 扩增后, 产物与芯片使用 BioMixer TMII 四梯度杂交仪于 50℃ 恒温杂交 120 分钟, 取出芯片采用 LuxScan TM10K-B 扫描仪读取结果。微阵列芯片结核分枝杆菌耐药检测可检测利福平耐药基因 *rpoB* (511、513、516、526、

- > C) 和 *rpoB* (511 (T - > C) *katG* (315 (G - > C) 突变为 1 株, 分别占 2.27%。详见表 4。
变为主, 分别占 52.27%、18.18% 和 9.09%, 其他突

表 2 不同农业景观区域肺结核患者耐利福平、耐异烟肼及耐多药的情况

Table 2 Prevalence of rifampicin resistance, isoniazid resistance and multidrug resistance among pulmonary tuberculosis patients in different agricultural landscape areas

地区	总患者 [例(率,%)]	敏感患者 [例(率,%)]	耐药患者[例(率,%)]					
			总耐药	χ^2 值	<i>P</i> 值	利福平耐药	χ^2 值	<i>P</i> 值
农区	129(16.27)	107(82.95)	22(17.05)	2.231	0.328	18(13.95)	3.615	0.164
牧区	129(16.27)	111(86.05)	18(13.95)			10(7.75)		
半农半牧地区	535(67.47)	431(80.56)	104(19.44)			75(14.12)		
合计	793(100.00)	649(81.84)	144(18.16)			103(12.99)		
地区	总患者 [例(率,%)]	敏感患者 [例(率,%)]	耐药患者[例(率,%)]					
			异烟肼耐药	χ^2 值	<i>P</i> 值	耐多药	χ^2 值	<i>P</i> 值
农区	129(16.27)	107(82.95)	6(4.65)	9.089	0.011	2(1.55)	13.680	0.001
牧区	129(16.27)	111(86.05)	9(6.98)			1(0.78)		
半农半牧地区	535(67.47)	431(80.56)	70(13.08)			41(7.66)		
合计	793(100.00)	649(81.84)	85(10.70)			44(5.55)		

表 3 耐药患者利福平、异烟肼耐药的相关基因突变情况

Table 3 Gene mutations associated with rifampicin and isoniazid resistance in drug-resistant tuberculosis patients

药品	耐药菌株数	耐药基因	突变类型	突变菌株数	突变率(%)
利福平	103	<i>rpoB</i>	511(T - > C)	19	18.45
			513(C - > A)	1	0.97
			516(A - > G)	5	4.85
			516(A - > T)	4	3.88
			516(G - > T)	26	25.24
			526(A - > T)	2	1.94
			526(C - > G)	4	3.88
			526(C - > T)	11	10.68
			531(C - > T)	34	33.01
			533(T - > C)	4	3.88
异烟肼	85	<i>katG</i>	315(G - > A)	7	8.24
			315(G - > C)	72	84.71
		<i>inhA</i>	-15(C - > T)	7	8.24

表 4 耐多药患者耐药相关基因突变情况

Table 4 Drug resistance-related gene mutations in multidrug-resistant tuberculosis patients

突变类型	菌株数	突变率(%)
<i>rpoB</i> (511(T - > C) 516(A - > G) <i>katG</i> (315(G - > A)	1	2.27
<i>rpoB</i> (511(T - > C) 516(A - > G) <i>katG</i> (315(G - > C)	1	2.27
<i>rpoB</i> (511(T - > C) <i>katG</i> (315(G - > C)	4	9.09
<i>rpoB</i> (516(A - > T) <i>katG</i> (315(G - > A)	1	2.27
<i>rpoB</i> (516(A - > T) <i>katG</i> (315(G - > C)	1	2.27
<i>rpoB</i> (516(G - > T) <i>katG</i> (315(G - > C)	23	52.27
<i>rpoB</i> (516(G - > T) <i>katG</i> (315(G - > C)	1	2.27
<i>rpoB</i> (526(C - > T) <i>inhA</i> (-15(C - > T)	1	2.27
<i>rpoB</i> (531(C - > T) <i>katG</i> (315(G - > A)	1	2.27
<i>rpoB</i> (531(C - > T) <i>katG</i> (315(G - > C)	8	18.18
<i>rpoB</i> (533(T - > C) <i>katG</i> (315(G - > A)	1	2.27
<i>rpoB</i> (533(T - > C) <i>katG</i> (315(G - > C)	1	2.27

3 讨论

本研究中, 甘孜州利福平耐药率和异烟肼耐药率

分别为 12.99% 和 10.70%, 分别远高于四川省平均水平(分别为 5.09% 和 8.96%)^[11], 以及省内泸州市耐药情况(分别为 4.49% 和 9.80%)^[12]。其利福平耐药率虽比省内遂宁高(8.39%), 异烟肼耐药率却低于遂宁(11.33%)^[13]。不过, 利福平、异烟肼两种药物耐药率低于西藏地区平均水平(分别为 11.15% 和 14.08%)^[14]。甘孜州结核病耐多药率为 5.55%, 高于四川省的 3.67%^[11], 也高于同省遂宁市的 5.13% 和泸州市的 3.47%^[12-13], 但低于西藏地区的 7.68%^[14]。甘孜州结核病耐药形势严峻, 应加强患者规范化治疗和管理, 减少患者因不规范治疗产生继发性耐药和因传播导致原发性耐药。现有研究显示国内异烟肼耐药发生率高于利福平^[15], 且全球异烟肼耐药率高于利福平^[16], 这可能与分子耐药检测时广泛检测利福平耐药基因, 而异烟肼耐药检测较少, 导致利福平耐药患者比异烟肼耐药患者获得更多关注, 利福平耐药更被重视有关^[17-18]。而甘孜州利福平耐药率高于异烟肼, 可能与该地区分子耐药检测未

大规模开展,利福平耐药检测较少,耐药患者发现不足和规范化治疗不足有关,这也导致该地区利福平、异烟肼耐药率远高于四川省水平。

不同年龄组患者中,0 ~ <20 岁组人群耐多药率最高,达到 6.90%。该地区地域偏远,耐多药患者接受规范治疗和治愈率低,特别是低龄人群更易因抗结核药物服药周期长、存在肠道反应和肝肾功损伤等不良反应而擅自停药,不规范治疗诱导耐药产生,而低龄人群主要活动于学校这种人员密集场所,更易导致耐药菌株在同龄人群间传播,使该年龄人群耐多药突出^[19-20]。因此,更需加强低龄人群耐多药患者管理,使其规范治疗,并重视学生人群结核病筛查、治疗和管理,减少结核耐药产生和传播。

甘孜州农业景观分为农区、半农半牧区、牧区。总耐药率、利福平耐药率、耐多药率以半农半牧地区最高,牧区最低,异烟肼耐药以半农半牧区最高,农区最低。农区主要分布于甘孜州东南部,交通便利,经济条件较好,牧区则集中于西北部,海拔高,气候严寒,交通不便,地广人稀,经济发展滞后。半农半牧区地理位置则介于二者之间,其各项条件亦处于二者过渡状态。受地理环境与交通条件影响,可能导致牧区患者就医难度大,半农半牧地区就医存在一定困难,农区患者则最易接受规范化治疗。基于上述区域差异推测,半农半牧区结核病患者虽具备一定就医可及性,但难以获得规范系统的治疗,进而可能导致该区域患者耐药情况最为严重。在结核病防治工作中,应重点加强半农半牧地区的患者管理,提高规范化治疗率,从而降低耐药情况。

该地区利福平耐药基因突变以 531 (C - > T) 为主,占 33.01%,这与四川省^[21]及省内眉山^[22]、遂宁^[13]一致,也与福建厦门^[23]、龙岩^[24]以及上海^[25-26]等地一致。531、526、513、511 位点突变与利福平中、高水平耐药相关^[27],在本研究中,526 位点突变占 16.50%,513 位点突变占 0.97%,511 位点突变占 18.45%,三个位点突变共占 68.93%;516、533 位点密码子突变一般导致低水平耐药^[28],共占 37.86%,说明该地区利福平耐药突变主要集中在中高水平耐药突变。据研究,异烟肼耐药突变位点以 *KatG*315 和 *inhA*-15 位点为主,*katG*315 突变占 42% 至 95%,*inhA*-15 突变占 6% 至 43%,而 315 位点突变易与高水平耐药相关^[29-30]。本研究中异烟肼耐药基因突变主要集中在 *KatG*315 (G - > C)、315 (G - > A) 和 *inhA*-15 (C - > T),分别占 84.71%、8.24% 和 8.24%,315 位点突变共占 92.94%,与全球及国内^[22-26]突变情况一致,以高水平耐药突变位点为主,提示需重点关注该地区 315 位点所致的异烟肼耐药。耐多药的

耐药突变中,以 *rpoB* (516 (G - > T)) *katG* (315 (G - > C)) 为主,占 52.27%,表现为利福平低水平耐药异烟肼高水平耐药。

针对甘孜州结核病利福平异烟肼耐药高的问题,该地区更应加强县域内患者分子耐药检测,缩短耐药检测时间,将检测出的耐药患者第一时间转诊至耐药结核病定点医院治疗,规范用药,并加强耐药患者管理,增加治疗成功率,减少耐药结核病传播。最终助力实现“消除结核危害、保障藏区人民健康”的核心目标,为健康中国战略在高原藏区的落地提供实践支撑。

利益冲突声明 本研究不存在任何利益冲突

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