Journal of Infectious Diseases & Therapy
ISSN: 2332-0877

Research Article Open Access

Impact of MicroRNA (*miR453, miR608, miR499, miR423*) on the Risk of Developing MDR-TB in an Amazonian Mixed-Race Population

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Abstract

Tuberculosis (TB) continues to be a major global health problem, with the emergence and spread of Multidrug-Resistant Tuberculosis (MDR-TB). Genetic factors play a significant role in determining susceptibility to TB and the development of drug resistance. Brazil is in one of the most genetically diverse populations in the world due to the high mix between Amerindian, African and European populations, which makes this population unique in relation to the world for genomic studies. This study aimed to investigate the genotypic differences in MDR-TB-associated variants and their potential implications as genetic markers for these conditions in a Brazilian Amazon population with a high degree of admixture. This case-control study was conducted on 190 subjects, including 165 TB patients and 25 MDR-TB patients. The case group was composed of individuals diagnosed with MDR-TB, while the control group was composed of TB patients at the João Barros Barreto Hospital, in Belém (Pará-Basil). Statistical tests revealed significant differences in African ancestry between MDR-TB groups. The results regarding the investigated SNVs were significant for the risk of developing MDR-TB for mRNA: *miR453* rs56103835, *miR608* rs4919510, *miR499* rs3746444 and *miR423* rs6505162. These Single-Nucleotide Polymorphism (SNVs) should be better investigated in subsequent studies with larger populations, as the population found in this study was small, which may have limited the causal relationships; in this way, new research can map populations susceptible to severe forms of tuberculosis. With the aim of applying new, more effective and individualized diagnostic means, based on genomics, contributing to reducing the socioeconomic impact in countries affected by forms of multidrug-resistant tuberculosis, equipping governments and public policies to identify susceptible people, monitor the treatment and avoid wasting time and resources.

Keywords: Genetic variation; Mix population; Multidrug-resistant tuberculosis

Introduction

Tuberculosis (TB) continues to be a major global health concern, with the emergence and spread of Multidrug-Resistant Tuberculosis (MDR-TB) posing additional challenges to TB control efforts [1]. Understanding the epidemiology of MDR-TB and its associated mortality is important for developing effective prevention and treatment strategies [2]. It is important to provide an overview of the epidemiology of MDR-TB globally and in Brazil, highlighting the differences in epidemiological patterns and exploring the causes of MDR-TB, including the influence of genetic variables [3].

MDR-TB is a form of TB caused by strains of *Mycobacterium tuberculosis* that are resistant to at least two of the most potent anti-TB drugs, isoniazid and rifampicin. According to the World Health Organization (WHO), an estimated 465,000 people worldwide developed MDR-TB in 2020 [4]. The highest burden of MDR-TB is observed in countries with high TB incidence rates, inadequate healthcare systems and limited access to diagnostic tools and effective treatments. Regions such as Eastern Europe, Central Asia and parts of Africa have reported the highest rates of MDR-TB [4].

The prevalence of MDR-TB varies across different regions. According to the Brazilian Ministry of Health, approximately 10% of TB cases in Brazil are estimated to be resistant to at least one anti-TB drug, with MDR-TB rates ranging from 1% to 3% among new cases and 10% to 20% among previously treated cases. The higher rates of MDR-TB can be attributed to various factors, including inadequate TB control measures, limited access to healthcare, insufficient laboratory capacity for accurate diagnosis, incomplete treatment and poor treatment adherence [5,6].

TB, including MDR-TB, is a leading cause of mortality worldwide. In 2022, an estimated 1.6 million people died from TB-related causes globally [7]. Mortality rates are influenced by factors such as the availability of quality healthcare, early detection and diagnosis, access to effective treatment and comorbidities such as HIV infection. MDR-TB is associated with higher mortality rates compared to drug-suscetible TB, as its treatment is more complex and less effective [8]. MDR-TB contributes to a higher mortality rate compared to drug-susceptible TB [6,7], emphasizing the need for improved strategies for early detection, accurate diagnosis and effective treatment of MDR-TB cases [4,6,9].

Certain populations, such as individuals with HIV co-infection, immunocompromised individuals are more susceptible to MDR-TB. Socioeconomic factors, including poverty, malnutrition, access to quality diagnostic tools and treatment and population dynamics, also contribute to the higher prevalence of MDR-TB in certain populations [8,10]. These disparities can impact the epidemiological patterns of MDR-TB across different regions [10,11]. Brazil is one of the populations with the greatest genetic diversity in the world due to the high mixing between Amerindian, African and European populations, which makes this population unique in relation to the world for genomic studies [11-13].

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Received: 28-Aug-2024, Manuscript No. JIDT-24-146722; **Editor assigned:** 31-Sep-2024, PreQC No. JIDT-24-146722 (PQ); **Reviewed:** 14-Sep-2024, QC No. JIDT-24-146722; **Revised:** 21-Sep-2024, Manuscript No. JIDT-24-146722 (R); **Published:** 28-Sep-2024, DOI: 10.4173/2332-0877.24.S8.002

Citation: Athayde AC, Leal DF, Pastana LF, Fernandes MR, Coelho RD, et al. (2024) Impact of MicroRNA (*miR453, miR608, miR499, miR423*) on the Risk of Developing MDR-TB in an Amazonian Mixed-Race Population. J Infect Dis Ther 12:002.

Genetic factors play a significant role in determining susceptibility to tuberculosis and the development of drug resistance. Specific genetic variations have been associated with an increased risk of developing TB, such as mutations in genes involved in drug metabolism and immune response [12]. Variations in drug targets and pathways can affect the efficacy of anti-TB drugs, leading to drug resistance. Additionally, host genetic factors may influence the immune response to TB infection and the likelihood of developing drug resistance [13].

The identification of Single Nucleotide Variants (SNV) in the miRNA pathway is emerging as a powerful tool for studying the molecular biology of diseases and has potential to aid prognosis and diagnosis [14]. The detection of miRNA variants is promising in the field of personalized medicine in order to predict the behavior of medicines in individuals differently, for better effectiveness in the treatment of infectious diseases, as well as cancer, neurological disorders, muscular atrophy, atrophy of the gastric mucosa, in cardiovascular diseases and type II diabetes [15,16].

Genotype-phenotype interaction studies make it possible to investigate a possible relationship between genetic variants and the development of diseases using statistical correlations to identify the effect of these variants and which may allow finding markers capable of reflecting the effect of risk or protection in complex pathologies. such as tuberculosis, which has several clinical outcomes and with several genes that may be involved in the evolution of the disease to severe and difficult to treat forms and to forms of multidrug resistance, where SNV in microRNA immune and inflammatory response genes and biogenesis machinery, may be associated with this risk [13,15].

Understanding the epidemiology of MDR-TB and its associated mortality rates is major for developing effective strategies to control and prevent the spread of drug-resistant strains. Brazil, like many other countries, faces challenges in tackling MDR-TB due to socioeconomic disparities, inadequate healthcare infrastructure and regional variations in TB control efforts. Genetic variables, including variations in host immune response genes, play a significant role in the development and spread of MDR-TB [3,15].

This study aimed to investigate the genotypic differences in variants associated with MDR-TB and their potential implications as genetic markers for these conditions in a population in the Brazilian Amazon with a high degree of admixture.

Materials and Methods

Subjects

This case control study was performed on 190 individuals, including 165 TB patients and 25 MDR-TB patients, evaluated in the period from 2019 to 2020 in the Tuberculosis program of the Hospital João Barros Barreto in Belém/Pará, Brazil, screened through sensitivity or resistance testing, primary or secondary to first-line drugs in sputum or bronchial lavage culture or tissue biopsy material. The case group consisted of individuals diagnosed with MDR-TB, while the control group comprised TB patients. The patients were diagnosed with TB and MDR-TB was based on clinical, radiological, sputum Acid-Fast Bacillus (AFB) smear positivity and/or culture for a minimum of 6 months in, after having been accompanied in the basic network by nurses and doctors for monitoring consultations, prescriptions and receiving medications. Ancestry and genetic variations were analyzed using statistical tests to determine significant differences in the distribution of genotypes. Additionally, demographic data, including age and sex, were examined for potential associations.

Committee for research ethics

The research protocol received approval from the Committee for Research Ethics of the Federal University of Pará (approval no. 42106720.2.0000.5634). All participants provided their informed consent by signing the free and informed consent form before participating in the study.

DNA extraction

Peripheral blood samples from subjects were collected using Ethylenediamine Tetraacetic Acid (EDTA)-coated tubes. Genomic DNA was then extracted from 200 µL of peripheral whole blood samples using the mini spin plus extraction kit (BioPur, Curitiba, Paraná, BR) following the manufacturer's instructions. The concentration of DNA samples was determined using spectrophotometry at 260 nm with the nanodrop 2000 device (nanodrop technologies, Wilmington, DE, USA). The purity of the DNA was assessed by calculating the ratio of absorbance at 260 nm to 280 nm, which indicates DNA quality.

SNP genotyping

The choice of the genotypes studied was based on previous studies by the team, which identified as significant for the susceptibility of tuberculosis, which are: *DROSHA* (rs10035440), *DROSHA* (rs639174), *miR453* (rs56103835), *miR2053* (rs10505168), *miR300* (rs12894467), *miR146A* (rs2910164), *miR196A2* (rs11614913), *miR149* (rs2292832), *AGO01* (rs636832), *miR200B/200A/429* (rs9660710), *miR20b/miR175P* (rs3660), *miR608* (rs4919510), *miR499* (rs3746444), *miR605* (rs2043556), *miR570* (rs4143815), *miR200C* (rs12904), *pri-let-7a-1* (rs10739971), *miR219* (rs107822), *miR604* (rs2368392), *miR26-A1* (rs7372209), *miR100* (rs1834306), *miR4513* (rs2168518), *miR423* (rs6505162). These SNPs have not been previously associated with mortality of TB-MDR rate.

These candidate SNPs were selected according to studies in the PubMed database (www.ncbi.n/m.nih.gov/, accessed on 1st January, 2019). A total of 23 single nucleotide polymorphism were selected. The miRNAs were chosen based on previous studies demonstrating their involvement in biological processes and immune responses, regulating inflammatory responses. Additionally, these miRNAs were relevant to infectious diseases, as reported in tuberculosis and leprosy [14].

The genotyping of polymorphisms was performed using TaqMan openarray technology on the quantstudio™12K flex real-time PCR system (Thermo fisher scientific, Waltham, MA, USA), following the manufacturer's protocol. Sample preparation were performed including 2 µL of DNA (50 mg/ml) and 2 µL of TaqMan® openarray® genotyping master mix (Thermo, Carlsbad, CA, USA). The prepared samples were transferred to a customized openarray™ chip for real-time PCR amplification of target SNP regions. Data analysis was conducted using the TaqMan® genotyper software package (Thermo fisher scientific, Waltham, MA, USA). The format dictated the number of samples per run on the open array board. In format 32, there were 32 trials for 96 samples.

To ensure an adequate level of precision, polymorphisms were selected for further analysis according to three criteria: (i) MAF ≥ 1%; (ii) genotyping rate ≥ 80% and (iii) whether it was in Hardy-Weinberg Equilibrium (HWE). HWE was performed using Arlequin software v.3.5.1.2 (Institute of Ecology and Evolution, University of Bern, Switzerland). Once these criteria were applied, only 23 polymorphisms were selected for association analysis.

Ancestry informative markers

All participants are from the northern region of Brazil, which has a large ethnic mix between native Americans, Europeans and Africans, whose individual genetic contributions varied substantially between 5% and 47% for African genes, 16% and 86% for European genes and 9% and 68% for native American genes [11].

To estimate the ancestral proportions of the Amazon population, a panel of 61 Ancestry Informative Markers (AIMs) was employed. This AIM panel was previously described by Santos et al., and later expanded by Ramos et al., Brazil has a highly admixed population with European, African and native American ancestry and this panel of ancestry-specific markers was used to estimate individual and population genetic contributions [11,12].

Statistical analysis

Comparisons between the groups for categorical variants were performed using fisher's exact test and the Mann-Whitney test. Multiple logistic regression analyses were performed to estimate the Odds Ratio (OR) with a 95% confidence interval. The Hard-Weinberg equilibrium deviation with p-value and OR was determined by controlled logistic regression.

Differences in baseline characteristics, including age, sex and ancestry analysis, were compared using the exact test and Mann-Whitney tests. Associations between TB and MDR-TB were estimated by calculating Odds Ratios (ORs) and 95% Confidence Intervals (95% CI) using logistic regression analyses, adjusted for sex and ancestry. The ORs were defined in relation to the groups of cases, i.e., OR>1 represent an increased risk of MDR-TB [11]. A p-value<0.05 was considered statistically significant. Hardy-Weinberg Equilibrium ratio (HWE) tests with Bonferroni correction were used to evaluate the quality of genotype data.

Results

The Table 1 presents the distribution of epidemiological data and genetic ancestry in the TB and MDR-TB groups. The TB group consisted of 90 females (54.5%) and 75 males (45.5%), while the MDR-TB group had 12 females (48.0%) and 13 males (52.0%). The mean age of the TB group was 52.71 years and the MDR-TB group had a slightly lower mean age of 46.73 years.

The statistical analysis revealed a significant difference in African ancestry between the TB and MDR-TB groups. The TB group had a proportion of African ancestry of 0.34, while the MDR-TB group had a slightly lower proportion of 0.30.

Figure 1 demonstrates the ancestral composition analysis revealed differences between the TB and MDR-TB groups. The TB group had proportions of European (EUR), Native American (AMR) and African (AFR) ancestry of 0.25, 0.41 and 0.34 respectively. In the MDR-TB group, the proportions were 0.28 for EUR ancestry 0.42 for AMR ancestry and 0.30 for AFR ancestry. African genetic ancestry was not significant in multidrug-resistant tuberculosis, as it was in the general TB group.

Our results regarding the investigated SNVs are presented in Table 2 with 23 mutations in genes related to miRNA pathways where we found significance for only four (*miR453* rs56103835, *miR608* rs4919510, *miR499* rs3746444 and *miR423* rs6505162), we highlight that two presented a risk effect for the development of the MDR-TB form and two had a protective effect.

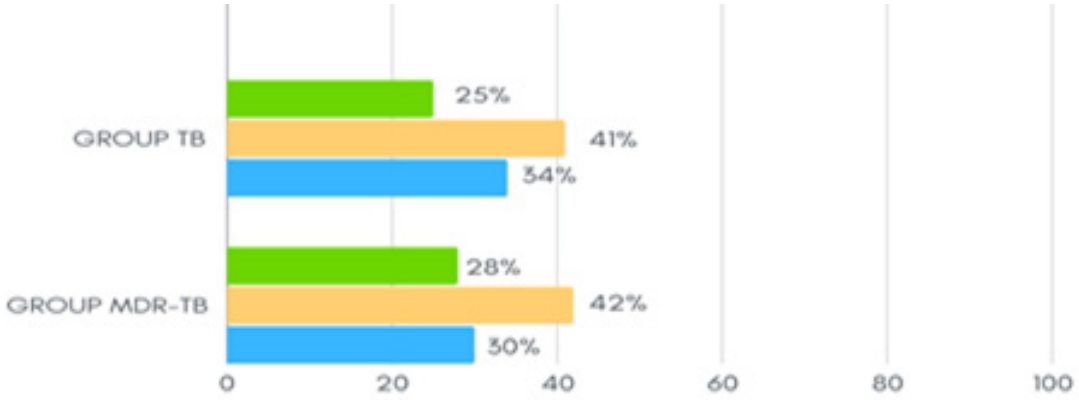

Figure 1: Genomic ancestry of Tuberculosis (TB) patients and Multidrug-Resistant Tuberculosis (MDR-TB) patients. **Note:** ( ) European; ( ) Native American; ( ) African

Variable	TB (n=165)	MDR-TB (n=25)	p-value
Sex[a]			
Female	90 (54.5%)	12 (48.0%)	0.668[c]
Male	75 (45.5%)	13 (52.0%)	
Age[b]	52.71 (49.7%-55.7%)	46.73 (41.9%-51.5%)	0.125[d]
Ancestry			
EUR[b]	0.25 (0.23-0.27)	0.28 (0.22-0.33)	0.204[d]
AMR[b]	0.41 (0.38-0.43)	0.42 (0.36-0.48)	0.326[d]

AFRb	0.34 (0.31-0.36)	0.30 (0.24-0.34)	0.035[d]

Note: TB: Tuberculosis; MDR-TB: Multidrug-Resistant Tuberculosis; [a] Frequency distribution of sexes; [b] Mean (95% CI); [c] Fisher's exact test and d Mann-Whitney test.

Table 1: Distribution of epidemiological data and genetic ancestry in TB and MDR-TB groups.

	TB (%)	MDR-TB (%)	p-value[c]	OR (IC 95%)
Genotype (SNP ID)				
miR146A (rs2910164)	n=114	n=17	0.559	0.731 (0.25-2.09)[b]
CC	13 (11.4%)	0 (0%)		
CG	49 (43.0%)	10 (58.8%)		
GG	52 (45.6%)	7 (41.2%)		
miR4513 (rs2168518)	n=112	n=13	0.619	0.74 (0.23-2.39)[b]
AA	8 (7.1%)	1 (7.7%)		
AG	45 (40.2%)	6 (46.2%)		
GG	59 (52.7%)	6 (46.2%)		
miR499 (rs3746444)	n=110	n=17	0.049*	0.022 (0.001-0.97)[a]
AA	0 (0%)	0 (0%)		
AG	25 (22.7%)	6 (35.3%)		
GG	85 (77.3%)	11 (64.7%)		
miR100 (rs1834306)	n=110	n=13	0.705	1.41 (0.23-8.65)[a]
AA	89 (80.9%)	9 (69.2%)		
AG	21 (19.1%)	4 (30.8%)		
GG	0 (0%)	0 (0%)		
miR570 (rs4143815)	n=107	n=14	0.148	2.37 (0.73-7.63)[b]
CC	00 (0%)	00 (0%)		
CG	60 (56.1%)	5 (35.7%)		
GG	47 (43.9%)	9 (64.3%)		
miR608 (rs4919510)	n=104	n=12	0.03*	0.24 (0.06-0.87)[b]
CC	16 (15.4%)	5 (41.7%)		
CG	44 (42.3%)	2 (16.7%)		
GG	44 (42.3%)	5 (41.7%)		
miR604 (rs2368392)	n=101	n=12	0.928	1.06 (0.28-3.90)[b]
AA	43 (42.6%)	6 (50%)		
AG	52 (51.5%)	6 (50%)		
GG	6 (5.9%)	0 (0%)		
miR300 (rs12894467)	n=99	n=13	0.15	2.69 (6.99-10.36)[b]
CC	13 (13.2%)	4 (30.8%)		
CT	44 (44.4%)	2 (15.4%)		
TT	42 (42.4%)	7 (53.8%)		
AGO01 (rs636832)	n=96	n=09	0.089	4.30 (0.79-23.14)[b]
AA	15 (15.6%)	0 (0%)		
AG	43 (44.8%)	2 (22.2%)		
GG	38 (39.6%)	7 (77.8%)		
miR200C (rs12904)	n=96	n=10	0.419	1.95 (0.38-9.83)[a]
AA	33 (34.4%)	2 (20%)		
AG	38 (39.6%)	4 (40%)		
GG	25 (26.0%)	4 (40%)		
DROSHA (rs10035440)	n=93	n=14	0.403	0.610 (0.19-1.94)[a]
CC	29 (31.2%)	06 (42.9%)		
CT	64 (68.8%)	08 (57.1%)		
TT	0 (0%)	0 (0%)		
miR196A2 (rs11614913)	n=87	n=09	0.359	3.06 (0.28-33.59)[b]
CC	46 (52.9%)	04 (44.4%)		
CT	37 (42.5%)	04 (44.4%)		
TT	04 (4.6%)	01 (11.1%)		
pri-let-7a-1 (rs10739971)	n=84	n=07	0.162	3.23 (0.62-16.83)[a]
AA	66 (78.6%)	4 (57.1%)		
AG	15 (17.9%)	2 (28.6%)		
GG	3 (3.6%)	1 (14.3%)		

miR149 (rs2292832)	n=83	n=07	0.638	0.683 (0.13-3.34)[a]
TT	41(49.4%)	04 (57.1%)		
TC	28 (33.7%)	02 (28.6%)		
CC	14 (16.9%)	01 (14.3%)		
miR219-1 (rs107822)	n=78	n=12	0.196	3.31 (0.54-20.27)[b]
CC	44 (56.4%)	6 (50.0%)		
CT	29 (37.2%)	4 (33.3%)		
TT	5 (6.4%)	2 (16.7%)		
DROSHA (rs639174)	n=76	n=08	0.112	0.293 (0.06-1.33)[a]
CC	25 (32.9%)	05 (62.5%)		
CT	41 (53.9%)	01 (12.5%)		
TT	10 (13.2%)	02 (25.0%)		
miR605 (rs2043556)	n=75	n=08	0.343	0.47 (0.10-2.23)[a]
CC	18 (24.0%)	3 (37.5%)		
CT	33 (44.0%)	2 (25.0%)		
TT	24 (32.0%)	3 (37.5%)		
miR20b/miR175P (rs3660)	n=73	n=156	0.999	-
CC	2 (3.1%)	0 (0%)		
CG	1 (1.5%)	0 (0%)		
GG	62 (95.4%)	8 (100%)		
miR200B/200A/429 (rs9660710)	n=71	n=06	0.412	2.73 (0.24-30.15)[b]
AA	4 (5.6%)	1 (16.7%)		
CA	67 (94.4%)	5 (83.3%)		
CC	0	0		
miR26-A1 (rs7372209)	n=70	n=06	0.57	0.70 (0.21-2.32)[a]
CC	33 (47.1%)	2 (33.3%)		
CT	27 (38.6%)	4 (66.7%)		
TT	10 (14.3%)	0 (0%)		
miR453 (rs56103835)	n=66	n=09	0.048*	5.39 (1.01-28.79)[a]
CC	06 (9.1%)	03 (33.4%)		
CT	31 (47.0%)	02 (22.2%)		
TT	29 (43.9%)	04 (44.4%)		
miR423 (rs6505162)	n=65	n=12	0.002*	14.03 (2.66-74.06)[a]
AA	3 (4.6%)	5 (41.7%)		
AC	48 (73.8%)	4 (33.3%)		
CC	14 (21.5%)	3 (25.0%)		
miR2053 (rs10505168)	n=60	n=07	0.378	2.05 (0.41-10.21)[b]
CC	10 (16.7%)	0 (0%)		
CT	26 (43.3%)	03 (42.9%)		
TT	24 (40.0%)	04 (57.1%)		

Note: TB: Tuberculosis; MDR-TB: Multidrug-Resistant Tuberculosis; *Significant p-value (<0.05); [a] Dominant model analysis; [b] Recessive model analysis and [c] Fisher's exact test.

Table 2: Genotypic distribution of SNV in the TB and MDR-TB groups in hardy-weinberg equilibrium with p-value and odds ratio determined by controlled binary logistic regression.

We can see that in *miR453* there is a risk in Colorectal Cancer (CC) homozygous individuals to develop the MDR-TB form. The p-value for this comparison was 0.048, indicating a statistically significant difference in genotype distribution. The OR was 5.39, suggesting an increased risk associated with the CC genotype in the MDR-TB group.

Another miRNA that presented risk was *miR423* (rs6505162). In the MDR-TB group, 5 (41.7%) of these individuals had the *AA* genotype and the p-value for this comparison was 0.002, indicating a statistically significant difference. The OR was 14.03, suggesting an increased risk associated with homozygous genotype in the MDR-TB group.

Regarding *miR608* (rs4919510), the p-value for this comparison was 0.031, indicating a statistically significant difference in genotypic distribution. The OR was 0.24, suggesting a protective effect associated with the *CC* genotype in the MDR-TB group. Lastly, for *miR499* (rs3746444), The p-value for this comparison was 0.049, indicating a statistically significant difference. The OR was 0.022, suggesting a protective effect associated with the *GG* genotype in the MDR-TB group [17].

Discussion

This work was designed based on the increase in registered cases of tuberculosis resistant to drugs usually used in the first line of treatment, such as rifampicin and isoniazid and the threat to society of infection by these agents with a high risk of severity and mortality [18], we investigated the genotypic differences in genetic variants in microRNA associated with the cases of tuberculosis diagnosed in this sample and the possibility of associating them as markers of progression to multidrug-resistant tuberculosis.

Regarding ancestry, in this population, African ancestry was higher in the treatable TB group, which may indicate that these individuals would have a lower risk of developing the multidrug-resistant form of tuberculosis, thus being less prone to the more difficult-to-treat forms of tuberculosis. In the study by Leal et al., Amerindian ancestry was described as significant when compared to European and African; however, this sample consisted of patients with unspecified tuberculosis [13].

According to the results, four microRNA variants were found (*miR453* rs56103835, *miR608* rs4919510, *miR499* rs3746444 and *miR423* rs6505162), related to protection or risk of developing MDR-TB. However, there are still no publications that associate the genetic variants found with the development of tuberculosis to drug-resistant forms, especially in genetically mixed populations such as those in the Brazilian Amazon.

Regarding *miR453* rs56103835, the literature mentions that the deregulation of these miRNA occurs in other diseases studied, such as the risk of developing metastases in colorectal cancer, esophageal cancer and coronary artery disease [19,20]. Also cited as being responsible for the protective factor for gastrointestinal toxicity in pediatric All patients in the homozygous wild-type *TT* variant [21]. Our results for *miR453* (rs56103835) showed an increased risk of developing the multidrug-resistant form of tuberculosis, associated with the *CC* genotype.

For our study, *miR608* rs4919510 showed a protective effect in the MDR-TB group, in the *CG* genotype. However, it is indicated in the literature with a strong association of development and worsening of diseases as HBV; in cancer, such as esophageal carcinoma and with toxicity in cancer treatment; and even with protection against the development of colorectal cancer for the *GG* variant [22,23]. However, as our work is pioneering in MDR-TB, we did not find studies relating this microRNA to MDR-TB in another population.

The *miR499* rs3746444 was reported in other studies to be responsible for the risk of developing diseases such as acute lymphoblastic leukemia, asthma and rheumatoid arthritis [21,24,25]. This miRNA was investigated in a study in the Iranian population and did not show any significant changes in expression that could be related to pulmonary tuberculosis [26]. In this study we found a significant association of the protective effect for the MDR-TB group in the *GG* genotype.

Finally, regarding *miR423* rs6505162, in other studies, it has been related to diseases such as: The development of Type 2 Diabetes Mellitus (T2DM), colorectal cancer, recurrent pregnancy losses, hepatocellular carcinoma, acute myocardial infarction and wilms tumor in children [19,27-29]. A study demonstrated the relationship with pulmonary tuberculosis through the positive regulation of miR-423-5p, which could inhibit the maturation of the autophagosome-lysosome in macrophages through the post-transcriptional regulation of VPS33A, which could be important for the development of active tuberculosis [30]. In our study, there was a statistically significant difference for this miRNA and the risk of developing MDR-TB.

Effective control of TB and MDR-TB depends on early diagnosis, rapid and effective treatment, helping to reduce the side effects of using various medications and patient adherence to treatment. Given these needs, perhaps a rapid molecular test based on the host's genetics and not on that of the infectious agent like the current ones, could be more sensitive and accurate [31]. Our study identified two SNVs with potential risk for the development of drug-resistant forms of TB. Emerging as objects of other research for the development of personalized tests to predict potentially predisposed individuals.

Conclusion

This study identified genotypic differences in SNV associated with TB and MDR-TB. The distribution of African ancestry was significantly different between the TB and MDR-TB groups, suggesting a potential association with protection to multidrug-resistant tuberculosis.

Furthermore, significant differences were observed in the genotypic distribution of *miR453* rs56103835, *miR608* rs4919510, *miR499* rs3746444 and *miR423* rs6505162 between the TB and MDR-TB groups. Of these, *miR453* rs56103835 and *miR423* rs6505162 suggested an increased risk of developing the MDR-TB form.

These SNVs should be better investigated in subsequent studies with larger populations, as the population found in this study was small, which may have limited the causal relationships; in this way, new research can map populations susceptible to severe forms of tuberculosis. With the aim of applying new, more effective and individualized diagnostic means, based on genomics, contributing to reducing the socioeconomic impact in countries affected by forms of multidrug-resistant tuberculosis, equipping governments and public policies to identify susceptible people, monitor the treatment and avoid wasting time and resources.

Author Contributions

Article writing for Aidalucy do Socorro Costa de Athayde: Conceptualization, formal analysis, investigation, visualization, writing-original draft; Diana Feio da Veiga Borges Leal: Writing, investigation; Lucas Favacho Pastana: Formal analysis; Marianne Rodrigues Fernandes: Methodology, supervision; Rita de Cássia Calderaro Coelho: Visualization; Sidney Emanuel Batista dos Santos: Methodology, supervision; Paulo Pimentel de Assunção: Investigation; Ney Pereira Carneiro dos Santos: Investigation, writing and supervision. All autthors were involved in the final verson of the manuscript.

Data Availability Statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://doi.org/10.6084/m9.figshare.17954717.v2.

Acknowledgments

The autors wish to thank all the participants of the study for their collaboration. This study was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Universidade Federal do Pará (UFPA).

Conflicts of 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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