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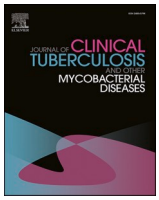

Analysis of the c.1135G > A, c.1993A > G, c.2059T > C *TAP2* gene variants and their relationship with latent tuberculosis infection in Mexico

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ABSTRACT

Tuberculosis (TB) is a worldwide public health problem with 10.6 million people falling ill and 1.5 million deaths every year. Latent tuberculosis infection (LTBI) is a condition in which an individual has been infected with *Mycobacterium tuberculosis* (*Mtb*) but does not show clinical signs and symptoms. The transporter associated with antigen processing (TAP2) protein plays a fundamental role in the immune response promoting the clearance of intracellular pathogens, such as *Mtb*. Our study aimed to determine the association between c.1135G > A (rs1800454), c.1993A > G (rs241447) and c.2059 T > C (rs241448) *TAP2* gene variants with LTBI susceptibility. In this case-control study, 180 individuals (90 were LTBI-positive and 90 were controls) from shelters were analyzed. Genotyping of the polymorphisms was performed using the Applied Biosystems Step One Thermal Cycler Real-Time PCR allelic discrimination technology. The haplotypic analyses were performed with the Arlequin 3.5 software. The G allele (OR = 1.732, CI = 1.125–2.667, $p = 0.012$) and AG genotype of the c.1993A > G variant (p=<0.001) were associated with susceptibility to LTBI (p=<0.001), as well as the GAT, AAT, AAC, AGT haplotypes (p=<0.001). The c.1135G > A and c.2059 T > C variants were not associated with LTBI risk.

1. Introduction

Tuberculosis (TB) is a public health problem and a threat to human health worldwide, more than 10 million people falling ill with tuberculosis and 1.5 million deaths every year. There is an estimated one-fourth of the population with latent tuberculosis infection (LTBI) [1].

Patients with LTBI have no clinical signs and symptoms of the disease, they maintain a persistent immune response to *Mycobacterium tuberculosis* (*Mtb*) antigens, and approximately 5–10 % of those infected will develop active TB at some point in their lives continuing with the disease transmission chain [2,3].

In Mexico, the incidence in 2023 was 20,794 TB cases. Therefore, in Mexico TB continues to be a public health challenge that will require promoting and reinforcing strategies against TB [4]. However, the prevalence of LTBI in Mexico is still unknown.

The risk of developing active TB is higher due to various factors such as living in overcrowded places such as orphanages, shelters, and jails. Other factors include malnutrition, illicit drugs users, prolonged use of corticosteroids, and exposure to TB in healthcare settings, especially in countries with high TB incidence and developing countries [5]. Besides, genetic factors have been linked to increased susceptibility to mycobacterial infections such as *VDR, IL12, IFNG, TAP* and *LMP7* gene polymorphisms [6–8].

Achieving an effective immune response against *Mtb* requires a balance between the innate and adaptive responses of the immune system. However, *Mtb* employs different virulence factors to avoid

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lysosomal degradation in macrophages that it infects. As a result, it can evade the MHC class II antigen presentation pathway and become resistant to host defense mechanisms [2,9]. Therefore, antigens are released into the cytosol, where they are processed via the ubiquitin–proteasome pathway with the involvement of LMP2/LMP7 proteins [10,11].

The antigenic peptides generated are transported to the lumen of the endoplasmic reticulum (ER) by TAP1/TAP2 proteins for cross-presentation [12]. Therefore, the cross-presentation is a critical mechanism for generating effective immune response to eliminate the bacillus on MHC class I mediated antigen presentation by CD8 + T cells [9,12]. Furthermore, the transporter associated with antigen processing (TAP) proteins are crucial for producing an effective immune response against intracellular pathogens and cancer cells.

The role of LTBI and its association with *TAP2* gene polymorphisms is unknown in the Mexican population. Therefore, this work aimed to determine the association of the rs241447 c.1993A > G (p.Thr665Ala, rs241447) c.2059 T > C, (p.Gln687Stop, rs241448), and c.1135G > A (p.Ile379Val, rs1800454) *TAP2* gene variants with LTBI susceptibility.

2. Materials and methods

2.1. Subjects and sample collection

A total of 192 participants were recruited from shelters offering social assistance in metropolitan areas of Guadalajara, Mexico, during 2019. Twelve of the 192 subjects were excluded because they did not fit the study criteria (comorbidities, such as HIV infection, diabetes mellitus, autoimmune diseases, and subjects with indeterminate QFT-Plus results). From the remaining 180 subjects, 90 were included in the group of cases all of whom were LTBI-positive and 90 subjects were included in the control group, without known records of TB exposure, a negative QuantiFERON-TB Gold Plus test, and no clinical or radiographic evidence of TB.

Blood was drawn from the case and control subjects, in ethylene diamine tetra-acetic acid (EDTA) and lithium heparin tubes, for DNA extraction and evaluation with the QuantiFERON-TB Gold Plus (QFT-Plus) test.

2.2. Ethical consideration

The present study was reviewed and approved by the Ethical and Biosecurity committee of the University Center of Health Sciences at the University of Guadalajara (Reference Number CI-04218; Guadalajara, Mexico). The research was performed according to the Brazil 2013 amendment of the Declaration of Helsinki (World Medical Association, 2013), the Council for International Organizations of Medical Sciences (CIOMS), and Mexico regulations for the studies on human health. Informed consent was signed by all the individuals included in the study.

2.3. LTBI evaluation

An assessment of LTBI was carried out using an interferon-gamma release assay (IGRA), using QFT-Plus (QIAGEN, Hilden, GERMANY) to measure the IFN-γ response of T-cells to the ESAT-6 and CFP-10 peptide antigens. Blood containing lithium heparin as an anticoagulant was transferred to the QFT-Plus tubes (Nil tube, TB1 tube, TB2 tube, and a Mitogen tube). A test was considered positive when the four tubes (Nil, TB1, TB2, Mitogen), either the TB1 tube or the TB2 tube, were above the Nil IFN-γ IU/mL value. Subjects were considered LTBI-positive if they had a positive QFT-Plus test with no clinical or radiological evidence of active TB disease.

2.4. DNA extraction

Genomic DNA was extracted from peripheral whole blood of the cases and controls, using the High Pure PCR Template Preparation Kit (Roche, Indianapolis, USA), according to the manufacturés protocol.

2.5. Gene variants

Amplification was carried out in a StepOneTM Thermal Cycler using 50 ng/μl of genomic DNA, PCR Master 2X, Primers and Taqman probes 20X, in a total volume of the PCR reaction of 10 μl. The identification was performed by allelic discrimination with Real-Time PCR with a temperature of 95° C (10 min) for denaturalization and 45 cycles of annealing and extension with temperatures of 95 °C (15 s) and 60 °C (1 min) respectively. Variants were identified using primers and TaqmanTM hydrolysis probes for each of the variants in their wild-type and mutated forms, using TAP2 gene ID rs241447 (c.1993A > G), Cat# 175701925_10, wild type variant primers: 5′ TCCTAGACCACCCGCGCGACTTGACAGACGTCGGACACTCGTTAGTG-GTCG3′, 3′GCTGGTGATTGCTCACAGGCTGCAGACAGTTCAGCGCGCC CACCAGATCCT5′, polymorphic variant primers: 5′TCCTAGAC CACCCGCGCGACTTGACGGACGTCGGACACTCGTTAGTGGTCG3′, 3′ GCTGGTGATTGCTCACAGGCTGCAGGCAGTTCAGCGCGCCCACCAGA-TCCT5′; TAP2 rs241448 (c.2059T > C), Cat# 2961793_10, wild type variant primers: 5′GCCCTTATCTCCAGGACAGGGAGGATCTCGACCCG TTCGAAGACGTCGAAC3′, 3′CAAGCTGCAGAAGCTTGCCCAGCTCTAGG AGGGACAGGACCTCTATTCCCG5′, polymorphic variant primers: 5′GCCCTTATCTCCAGGACAGGGAGGACCTCGACCCGTTCGAAGACGT-CGAAC3′, 3′CAAGCTGCAGAAGCTTGCCCAGCTCCAGGAGGGACAG GACCTCTATTCCCG5′; rs1800454 (c.1135G > A), Cat# 8848961_20, wild type variant primers: 5′GGTGAGACCATAGAATGGGA GGAATGCTCGTCCATGTTCCGCGCAAGGTCC3′, 3′CCTGGAACGCGC CTTGTACCTGCTCGTAAGGAGGGTAAGATACCAGAGTGG5′, polymorp hic variant primers: 5′GGTGAGACCATAGAATGGGAGGAATACTC GTCCATGTTCCGCGCAAGGTCC3′, 3′CCTGGAACGCGCCTTGTACCTG CTCATAAGGAGGGTAAGATACCAGAGTGG5′ (Applied BiosystemsTM, Foster City, USA). FastStart Essential DNA Probes Master (ROCHETM, REF 06402682001, Indianapolis, USA).

2.6. Statistical analysis

The genotypic and allelic frequencies of the variants were determined by direct counting. The Hardy-Weinberg equilibrium in the control group was determined using the chi-square test (X^2). The genotypes' distributions and allele frequencies of the variants in both groups (LTBI cases and controls) were analyzed using the X^2 test**.** Non-parametric quantitative determinations, odds ratio (OR), and 95 % confidence interval (95 % CI) were used to analyze the TAP2 gene polymorphisms with LTBI risk. To evaluate the effect of variants on LTBI, the genotype frequencies were evaluated using different genetic inheritance models and haplotypic analysis. The statistical analysis was performed using Arlequin version 3.5, SPSS Statistics 25.0 software, and OpenEpi.com Statcalc. Statistical significance was set at a $p < 0.05$, and statistical power was 80 %.

3. Results

3.1. Population characteristics

In total, 90 patients diagnosed with LTBI, and 90 control subjects were enrolled in this cases and control study. The mean age of the control subjects was 24.38 years and 37.2 years for the individuals with LTBI. The demographic parameters of LTBI patients and controls are shown in Table 1.

3.2. Association between TAP2 gene variants and LTBI

The genotypic and allelic frequencies of the *TAP2* (c.1135G > A, c.1993A > G, c.2059 T > C) gene variants in the LTBI cases and the

controls are shown in Tables 2 and 3. The genotype distribution of the variants in the controls was in the Hardy-Weinberg equilibrium (p = 0.164, p = 0.40, and p = 0.360 respectively). There were no statistical differences in the allele frequencies of the *TAP* c.1135G > A and c.2059 T > C gene variants between the LTBI cases and the control group.

Regarding the c.1993A > G variant, we observed that the G allele was present in 43.9 % of the cases, compared to 31.1 % in the controls, with a statistically significant difference (OR = 1.732, CI = 1.125—2.667, p = 0.012). Besides, there was a statistically significant difference in genotypic frequencies between the study groups (p < 0.001), having a greater frequency (74.4 %) the AG heterozygote genotype in the LTBI group compared with the control group (46.6 %), indicating that there is an association between the variant and LTBI susceptibility (Table 3).

Comparing the genotypic frequencies of both groups, using different inheritance models, we found statistically significant differences for the c.1993A > G variant (rs241447) under the dominant, codominant, and additive models. To determine which inheritance model best suited the behavior of the variant with respect to the disease, the Akaike information criterion was used, with the codominant model being the most appropriate (OR = 3.847, IC = 1.940–7.628, p < 0.001 (Table 4). These associations remained significative (p < 0.05) in the codominant and dominant models after analyzing the data by gender.

3.3. Haplotypes and linkage disequilibrium analysis

In the examination of haplotypes, we identified eight potential allele combinations (Table 5). The GGT haplotype was the most frequent within the study groups and four distinct haplotypes were linked to an increased risk of LTBI: AAT (OR 2.215; 95 % CI 1.026–4.403; p = 0.041), AAC (OR 7.846; 95 % CI 2.033–30.28; p = 0.001), AGT (OR 3.923; 95 % CI 1.08–14.25; p = 0.029) and GGT (OR 2.779; 95 % CI 1.526–5.061; p = 0.001), using the GAT haplotype as a reference (Table 5).

Additionally, the c. 1993 A > G variant showed a high linkage disequilibrium (D') with the c.2059 T > C (D' = 0.7574; r^2 = 0.1081).

4. Discussion

LTBI is an asymptomatic infection caused by *Mtb*, which is inactive within the body, maintaining a constant immune response [13]. In Mexico, the prevalence of LTBI is unknown, however, a study carried out in 2022 estimates a prevalence rate of approximately 25.86 % [14]. Furthermore, other studies carried out in Mexican patients with rheumatoid arthritis and cancer report a prevalence of 14 % and 31.2 % respectively [13,15]. It is important to mention that in the study carried out in cancer patients, the TST test was used, a methodology that can produce false positives if used in populations that have received the Bacille Calmette-Guérin (BCG) vaccine, as is the case in Mexico [15,16].

TAP proteins play a fundamental role in the immune response to promote the clearance of intracellular pathogens, such as *Mtb*, therefore polymorphisms in genes that code for these proteins can lead to low peptide translocation, altering the MHC-I pathway [9,17]. These results have been observed in TAP-deficient mice which are more susceptible to TB infection, highlighting the importance of TAP in protective immunity against *Mtb*. Studies have also shown that mice with disruptions in TAP have a deficiency in MHC class I molecules and CD8 + T cells and they show an increased susceptibility to TB [18,19].

The role that TAP2 has in antigen presentation plays a crucial role in TB. This intracellular bacillus is engulfed by macrophages and processed into peptides that interact with TAP2-TAP1 complex and then loaded onto MHC class I molecules, which induces cytotoxic T lymphocyte response which is essential for a successful resolution of the infection [18,20]. A study of *TAP2* polymorphisms in patients with leprosy showed that some alleles may preferentially transport disease associated mycobacterial peptides more efficiently than the others, therefore being available easily for presentation by MHC class I molecules to the CD8 + T lymphocytes [21]. This same phenomenon could be happening in the case of TB since the infection mechanism is similar in both pathologies.

Polymorphisms in *TAP2* gene have been associated with various diseases in addition to tuberculosis, such as rheumatoid arthritis, systemic lupus erythematosus, allergic rhinitis, diabetes mellitus, ankylosing spondylitis, dengue fever and hepatitis B viral infection [17,22]. Studies related with tuberculosis have been shown controversial results. In three different studies in China, *TAP2* gene variants have been associated with an increased risk of pulmonary tuberculosis. Similar results are observed in Koreans, in this population the variants have been associated not only with susceptibility to tuberculosis but also with its recurrence and extent of lung lesions. On the contrary, in the Indian population, variants in *TAP2* gene have been associated with a decrease in susceptibility [23–26].

Furthermore, there is no study in the Mexican population, so in the present study the association of c.1135G > A, c.1993A > G, c.2059 T > C TAP2 gene variants and their relationship with latent tuberculosis infection was analyzed.

Rs241447 (c.1993A > G) have shown associations with psoriasis, decreased cancer susceptibility, decreased risk of pulmonary tuberculosis and an increased risk of HIV-1 infection [27]. Regarding TB, the association of this polymorphism varies between populations. It shows no association in Japanese population, while in the Korean population there is a risk association [20,28]. In the present study it had a significant association with LTBI. This variant is located in exon 11 of the gene

Table 1
Demographic characteristics of study groups.

Characteristic	Cases (LTBI)	Control Subjects	*P*
N	90	90	
Gender, n (%)			
Male	52 (57.8 %)	47 (52.2 %)	0.179
Female	38 (42.2 %)	43 (47.8 %)	
Age (years)			
Mean	37.2	24.38	**<0.0001**
Range	1–62	1 – 68	
Age Grups			
Children 1–11*	17	20	1
Teenagers 12–20*	12	20	0.189
Adults > 21*	61	50	0.478

LTBI = latent tuberculosis infection; *Age in years. p < 0.05 were considered statistically significant.

Table 2
Distribution of allelic frequencies in study groups.

Polymorphism	Cases n %		Controls n %		OR	CI 95 %	*P*
rs1800454 c.1135 G > A							
G*	132	73.3	147	81.7		1	
A	48	26.7	33	18.3	1.620	0.981 – 2.675	0.058
Total	180	100	180	100			
rs241447 c.1993 A > G							
A*	101	56.1	124	68.9		1	
G	79	43.9	56	31.1	1.732	1.125 – 2.667	**0.012**
Total	180	100	180	100			
rs241448 c.2059 T > C							
T*	128	71.1	127	70.6		1	
C	52	28.9	53	29.4	0.992	(0.629 – 1.556)	0.973
Total	180	100	180	100			

**Reference category*, OR: *Odds ratio*, CI: confidence interval. p < 0.05 was considered statistically significant. Results highlighted in bold are statistically significant.

Table 3
Distribution and comparison of genotypic frequencies of study groups.

		TAP2 rs1800454			*TAP2* rs241447			*TAP2* rs241448		
		c.1135 G > A			c.1993 A > G			c.2059 T > C		
		GG*	GA	AA	AA*	AG	GG	TT*	TC	CC
Cases	**N**	53	26	11	17	67	6	44	40	6
	%	58.9	28.9	12.2	18.9	74.4	6.7	48.9	44.4	6.7
Total			90			90			90	
Controls	**N**	62	23	5	41	42	7	43	41	6
	%	68.9	25.6	5.6	45.6	46.7	7.8	47.8	45.6	6.7
Total			90			90			90	
P			0.333			**<0.001***			0.958	

* Reference category, $p < 0.05$ was considered statistically significant. Cases: subjects with LTBI. Controls: Controls subjects.

Table 4
Analysis of the inheritance models of the Snps in the *Tap2* gene in both study groups.

Model	Genotypes	Cases		Controls		OR	CI 95 %	*P*
		n	%	N	%			
c.1135 G > A								
Dominant	GG*	53	58.9	62	68.9		1	
	GA + AA	37	41.1	28	31.1	1.546	0.838 – 2.853	0.163
Recessive	GG + GA*	79	87.8	85	94.4		1	
	AA	11	12.2	5	5.6	2.367	0.787 – 7.116	0.116
Codominant	GG*	53	58.9	62	68.9		1	
	GA	26	28.9	23	25.6	1.322	0.677 – 2.585	0.413
	AA	11	12.2	5	5.6	2.574	0.841 – 7.879	0.089
Additive						1.133	0.873 – 1.471	0.347
c.1993 A > G								
Dominant	AA*	17	18.9	41	45.6		1	
	AG + GG	73	81.1	49	44.4	3.593	1.836 – 7.031	**<0.001***
Recessive	AA + AG*	84	93.3	83	92.2		1	
	GG	6	6.7	7	7.8	0.847	0.273 – 2.627	0.089
Codominant	AA*	17	18.9	41	45.6		1	
	AG	67	74.4	42	46.7	3.847	1.940 – 7.628	**<0.001***
	GG	6	6.7	7	7.8	2.067	0.605 – 7.061	0.241
Additive						2.451	1.411 – 4.260	**0.001**
c.2059 T > C								
Dominant	TT*	44	48.9	43	47.8		1	
	TC + CC	46	51.1	47	52.2	0.956	0.533 – 1.716	0.881
Recessive	TT + TC*	84	93.3	84	93.3		1	
	CC	6	6.7	6	6.7	1	0.310 – 3.226	1
Codominant	TT*	44	48.9	43	47.8		1	
	TC	40	44.4	41	45.6	0.953	0.520 – 1.747	0.877
	CC	6	6.7	6	6.7	0.977	0.292 – 3.268	0.970
Additive						0.872	0.622 – 1.222	0.425

*Reference category. Results highlighted in bold are statistically significant. $p < 0.05$ was considered statistically significant.
Abbreviations: CI: confidence interval; OR: odds ratio; SNPs: Single nucleotide polymorphism.

Table 5
Distribution of haplotypes frequencies in both study groups.

Haplotypes	Cases		Controls		OR	CI (95 %)	p
	N	%	N	%			
GAT	26	14.44	51	28.33	1		
GGT	68	37.78	48	26.67	2.779	1.526 – 5.061	0.001*
GAC	37	20.56	46	25.56	1.578	0.831 – 2.994	0.162
AAT	26	14.44	24	13.33	2.125	1.026 – 4.403	0.041*
AAC	12	6.67	3	1.67	7.846	2.033 – 30.28	0.001*
AGT	8	4.44	4	2.22	3.923	1.08 – 14.25	0.029*
GGC	1	0.06	4	2.22	0.490	0.052 – 4.613	0.526
AGC	2	1.11	0	0	–	–	–

* Reference category, $p < 0.05$ was considered statistically significant. Cases: subjects with LTBI. Controls: Controls subjects.

and codifies for a cytoplasmatic domain of the protein important for ATP binding and/or hydrolysis [29,27]. Studies have shown that this variant is involved in MHC I restricted antigen processing pathway [30]. It may influence the alternative splicing of TAP2 isoforms characterized by different carboxyl terminals therefore changing the efficiency and specificity of transport of different peptides, also it can suppress TAP2 production in an allelic-specific manner by creating a potential binding site for hasmiR-1270 [27].

Therefore, this work aimed to determine the association of the rs241447 c.1993A > G (p.Thr665Ala, rs241447) c.2059T > C, (p. Gln687Stop, rs241448), and c.1135G > A (p.Ile379Val, rs1800454) *TAP2* gene variants with LTBI susceptibility.

Rs1800454 (c.1135G > A) and rs241448 (c.2059T > C) did not showed association with LTBI. They are located in exon 5 and exon 11 of *TAP2* gene respectively. Rs1800454 polymorphism has been associated with susceptibility to HCV infection, increased risk of rheumatoid arthritis and dengue hemorrhagic fever [17,27,31]. This variant located in a transmembrane domain is found in a peptide-binding region that could be relevant to transport of antigen derived peptides [33]. The rs241448 polymorphism occurs only in humans not in any other vertebrates and creates a premature stop codon that produces a truncated polypeptide chain lacking the C-terminal 17 amino acids of the full-length sequence. This alteration has no effect on the stability of the molecule [32,33]. Despite of changing the length of the protein this alteration has no effect on the stability of the molecule and it is

considered as benign by bioinformatics analyses [32].

The haplotypes GAT, AAT, AAC, AGT showed and association with LTBI. It has been observed that the variant combination in *TAP2* may influence the process of antigen transport and presentation. Besides, the combination with variants in *TAP1* play a crucial role since both proteins form a heterodimer and this protein complex may be altered by these variants [19]. However, further studies that include variants of TAP1 and TAP2 genes are needed to explain the effects on the pathogenesis of *Mtb* in Mexican population since a previous study demonstrated the risk association of rs1135216 y rs1057141 TAP1 gene variants with LTBI in Mexico [34].

5. Conclusion

In summary, we found that individuals with the G allele, the AG genotype of the c.1993A > G variant and the GAT, AAT, AAC, AGT haplotypes are more susceptible to latent tuberculosis in Mexican population.

6. Ethics approval and consent to participate

The study was approved by the Ethical and Biosecurity committee of the University Center of Health Sciences at the University of Guadalajara (approved on June 22, 2018; dictum number: CUCS/CINV/248/18; Reference Number CI-04218; Guadalajara, Mexico) and all patients gave written informed consent which is available upon request. All personal information such as name or initials is not mentioned in the paper.

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Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

CRediT authorship contribution statement

Gerardo Cazarez-Navarro: Writing – original draft, Validation, Methodology, Investigation. **Ivan Hernández-Cañaveral:** Writing – original draft, Validation, Methodology, Investigation. **Ana Gabriela Colima-Fausto:** Writing – review & editing, Writing – original draft, Formal analysis. **Jaime Palomares-Marín:** Writing – original draft, Methodology. **Karel Licona-Lasteros:** Methodology, Formal analysis. **Ana Laura Pereira-Suarez:** Writing – review & editing, Visualization, Resources. **Sergio Yair Rodríguez-Preciado:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Conceptualization.

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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