The Relationship of TLR2 Polymorphisms with Infectious Diseases

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ABSTRACT

The proinflammatory response induced by Toll-Like receptors (TLR) is considered the host's first defense line. Single nucleotide polymorphisms (SNPs) correspond to the most frequent type of variation in the human genome, and due to the importance of TLR2 in the immune response, SNPs in the TLR gene are related to susceptibility or resistance to various diseases. Thus, the objective of the present study was to identify the polymorphisms existing in the TLR2 gene that may cause susceptibility or protection against infectious diseases. We conducted a systematic review of the literature in the databases Science Direct, National Library of Medicine National Institutes of Health of the USA (PUBMED), Cochrane Collaboration and Medical Literature Analysis and Retrieval System Online (MEDLINE) between 2000 to 2020. The search resulted in 32 articles, all of which in English. Thus, it was demonstrated that the related polymorphisms are extremely important for the identification of related pathologies, whether for the susceptibility or protection of the individual to the diseases, also being essential for the mechanisms of signal generation and immune responses, and finally indicating that a balance between activation and inactivating these receptors to prevent an excessive inflammatory or immune response.

Keywords: Toll-like receptors 2; Polymorphisms; Infectious diseases.

1. INTRODUCTION

Infectious diseases are the second leading cause of mortality worldwide and the main cause of years of life adjusted to global disability-adjusted life years (DALYs) (one DAYL is equivalent to the loss of one year of healthy life) [1]. Over the past 20 years, the incidence of infectious and parasitic diseases has shown an equal downward trend, although in the same period, the emergence of unknown infectious diseases and recurrence of eradicated ones has been observed [2].

In a population endemic for a given disease, some individuals are diagnosed with active infection, which may or may lead to a fatal outcome, while others are asymptomatic [3]. The reason for such different outcomes relies on distinct immune responses, mostly associated with that may be due to variation in the individual's genetic makeup, leading to an ineffective or proper immune response during infection. A series of studies in the past 50 years have demonstrated the major importance of host immunogenetics in susceptibility and resistance to several infections [3–5].

Toll-like receptors (TLRs) are highly conserved transmembrane proteins originally discovered in the 1990s, among insects of the Drosophila genus, and are essential for the protection of flies against fungal infections. In 1997, a homolog of the Toll protein in humans was identified and characterized, called the Toll-Like receptor. To date, ten human TLRs have been identified and classified (TLR1-10), each related with a specific function and microbial component [6–8].

The TLRs play a similar role to pattern recognition receptors (PRR) present on macrophages, dendritic cells and neutrophils (polymorphonuclear leukocytes or PMN), which are responsible for recognizing the molecular patterns associated with pathogens (PAMP) expressed by a wide

spectrum of infectious agents [6,7]. Thus, when combined with agonists, most TLRs (TLR3, 4, 5, 7, 8 and 9) signal by homodimerization. The members of the TLR2 subfamily (including TLR1, 2, 6 and 10) are unique by forming heterodimeric complexes that can detect an extremely diverse set of microbial molecules. The TLR1-TLR2 association recognizes PAMPs from Gram-positive bacteria, including lipoproteins, lipopeptides, peptidoglycans and lipoic acids. The TLR2-TLR6 association is responsible for the recognition of lipoteichoic acid found in the cell wall Gram-positive bacteria and zymosan (polysaccharide derived from fungi) [6,7,9–11].

The proinflammatory response induced by TLRs is considered the host's first line of defense. When a PAMP is recognized by a TLR, it promotes phosphorylation of the IκB and its degradation results in the nuclear transcription factor (NF-κB), which is translocated to the nucleus and induces inflammatory cytokines and adhesion molecules expression. The balance between activation and inactivation of TLRs prevents an excessive inflammatory or immune response, as occurs in chronic inflammatory and autoimmune diseases. The underactivity of TLRs may result in higher susceptibility to pathogens, while hyperactivity is associated with autoimmune diseases, and with the unregulated activation of the nuclear factor (NF-kB) as one of the main contributors cancer development [10,11].

The underactivity and overactivity of TLRs are related to gene expression, which can be altered by single nucleotide polymorphisms (SNPs). The SNPs can cause alteration in the binding sites affinity of promoter regions, transcription factors and splicing sites or even cause exchange of an amino acids, leading to variations in the protein structure and / or function [12].

SNPs correspond to the most frequent type of variation in the human genome affecting coding (exons) and/or non-coding (introns) [13]. SNPs in genomic coding regions are subdivided into synonyms (sSNP) and not synonyms (nsSNP). Synonymous (or silent) SNPs cause base changes without alteration of the encoded amino acid sequence. However, synonymous mutations can affect the protein conformation, thus altering its cell function, and can directly interfere in phenotypic characteristics of individual. Non-synonymous SNPs lead to base substitutions, which changes the amino acid sequence, and consequently affect the encoded protein function (missense), or generat stop codons (nonsense) [14].

The TLR2 gene is located in the cromossomo 4:q31.3, and due to its importance in the immune response, SNPs in the TLR2 gene are related to susceptibility or resistance to various diseases [15,16]. And, in this context, the following research question emerged: Which SNPs exist in the TLR2 gene that are associated with susceptibility or protection against infectious diseases?

2. METHODOLOGY

This is a systematic bibliographic review, which aims to describe in a theoretical and conceptual way the previously reported correlations between the TLR2 gene polymorphisms and infectious diseases.

The study followed the stages of formation: 1- Elaboration of the research question and problem; 2- Inclusion and exclusion criteria definitions; 3- Sampling (selection of scientific articles); 4- Review and analysis of articles and 5- Interpretation, discussion and presentation of the systematic review [17].]. The PICO (Population, Intervention, Comparation, Outcome) strategy was applied on the elaboration of research question, as this strategy this generates greater integration of results and resolution of the highlighted problem [18].

Therefore, the following question were listed: what are the SNPs in the TLR2 gene associated with infectious diseases mentioned in the literature? In addition, the following characteristics were considered: Patient: patients with infectious diseases, Intervention: Evaluate the occurrence of TLR2 gene SNPs in infectious diseases, Comparison: Infectious diseases and TLR2 gene SNPs, and Outcome: Identification of TLR2 SNPs associated with susceptibility or protection to infectious diseases cited in the literature.

Identification and selection of articles was performed using the keywords: “TLR2”, “Polymorphisms”, “Infectious Diseases”, together with the Boolean operator “AND” in the

following databases: Science Direct, National Library of Medicine National Institutes of Health of the USA (PUBMED), Cochrane Collaboration and Medical Literature Analysis and Retrieval System Online (MEDLINE).

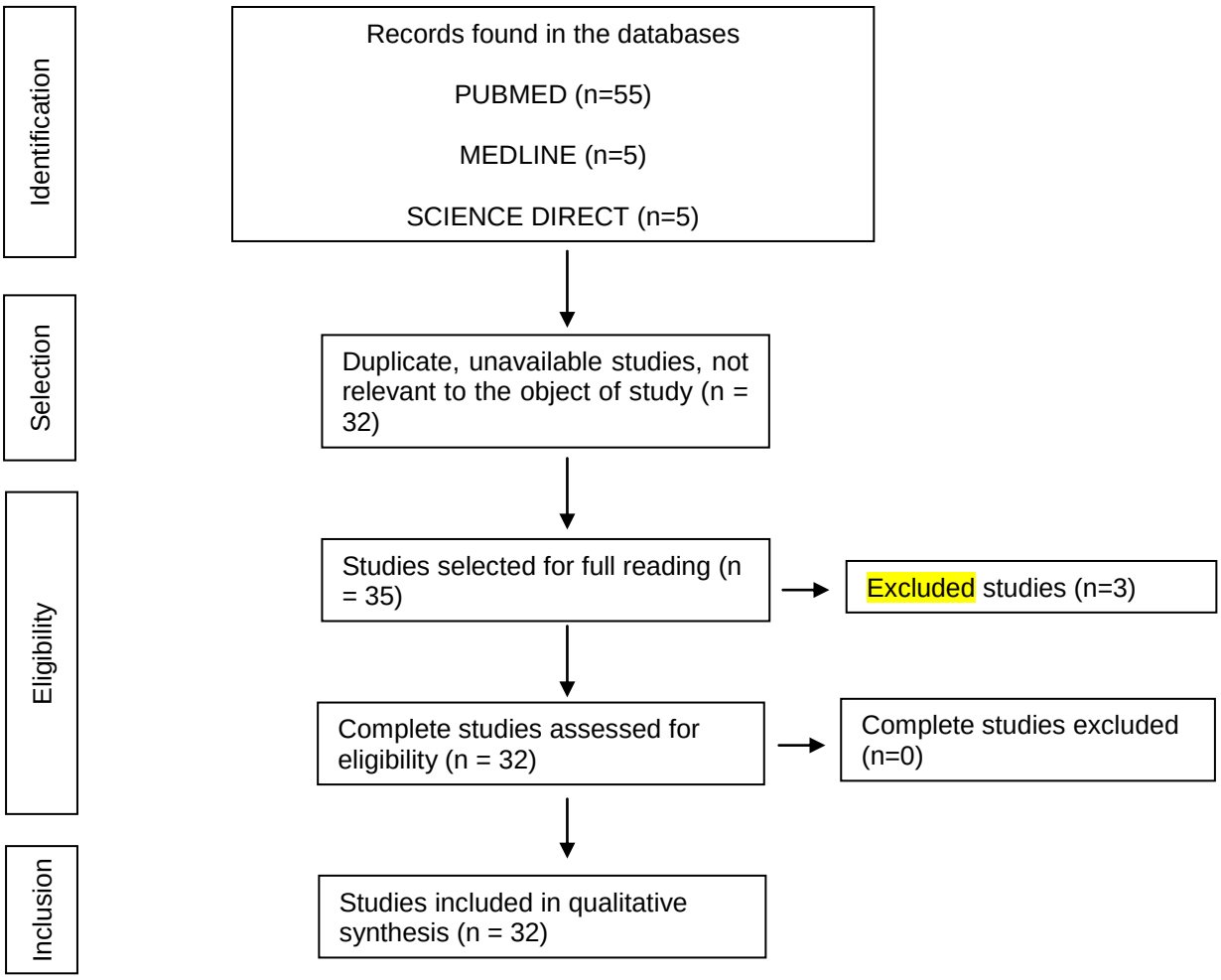
Inclusion criteria considered: articles published between 2000 and 2020, available as complete, original, systematic reviews, multicenter studies, case series, control cases, clinical trials, comparative, cohort studies, retrospective, prospective cohort studies, meta-analyses. Articles published prior to the year 2000, unpublished (abstract only), letters to the editor and non-relevant to the research question were excluded from analysis. In the extraction of data, a form consisting including selected variables was developed, including: title, database, methodology/ population size, country of study population, SNP and results.

PRISMA flowchart tool, based on PRISMA protocol was used to present the steps followed by the present study [19,20].

3. RESULTS

A total of 67 articles were retrieved, however, 35 of which were excluded, due to duplicity, letters to the editor or bring non-relevant topics to the research question (Fig. 1). Therefore, the final sample consisted of 32 articles (Table 1). Articles were mostly published in international journals (31), while one in national journal. Included articles were found in Science Direct, MEDLINE and PUBMED databases.

Fig. 1. Flowchart on the procedure for selecting studies, identification and eligibility for analysis. Belém, PA, Brazil, 2020.



1 **Table 1. Characteristics of studies included in the systematic review.**
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Title	Database	Methodology/ Population Size	Country	SNP	Results
Toll-like receptor 2 Arg677Trp polymorphism is associated with susceptibility to tuberculosis in Tunisian patients [21].	PUBMED	Comparative study/ 66 subjects, including 33 patients and 33 controls.	Tunisia	rs121917864.	The allele (T) variant was associated with tuberculosis.
Detection of Toll-like receptor 2 (TLR2) mutation in the lepromatous leprosy patients [22].	PUBMED	Case-control/ 131 subjects, including 45 lepromatous and 41 tuberculoid leprosy patients	South Korea	rs121917864; rs5743704.	For the SNP rs121817864, the allele (T) variant was associated with leprosy per se and lepromatous leprosy. For the SNP rs5743704, the (T) allele variant was associated with susceptibility to Virchowian leprosy.

Title	Database	Methodology/ Population Size	Country	SNP	Results
		and 45 controls.			
A Novel Polymorphism in the Toll-Like Receptor 2 Gene and Its Potential Association with Staphylococcal Infection [23].	PUBMED	Case-control/ 164 subjects, with 73 healthy blood donors and 91 patients.	France	rs5743708.	The allele (A) variant was associated with susceptibility to septic shock by *Staphylococcus infection*.
The Arg753GLn polymorphism of the human Toll-like receptor 2 genes in tuberculosis disease [24].	PUBMED	Case-control, retrospective/ 267 people, including 151 patients and 116 controls.	Turkey	rs5743708.	The (A) variant allele was associated with susceptibility to tuberculosis.
Toll-like receptor 2 R753Q polymorphisms are associated with	PUBMED	Case-control/ 131 subjects,	Spain	rs5743708.	The allele (A) variant was associated with an increased risk of infective endocarditis.

Title	Database	Methodology/ Population Size	Country	SNP	Results
an increased risk of infective endocarditis [25].		with 65 patients and 66 controls.			
Heterozygous Arg753Gln polymorphism of human TLR-2 impairs immune activation by Borrelia burgdorferi and protects from late-stage Lyme disease [26].	PUBMED	Case-control/ 504 subjects, including 155 patients and 349 controls.	Germany	rs5743708.	The (A) allele variant was associated with protection against Lyme disease.
TLR-2 gene Arg753Gln polymorphism is strongly associated with acute rheumatic fever in children [27].	MEDLINE	Case-control/ 268 subjects, with 61 patients and 207 controls.	Turkey	rs5743708.	The (A) variant allele was associated with rheumatic fever in children caused by Gram-positive bacteria (β-hemolytic streptococci).
Association between Toll-like receptor 2 (TLR2) polymorphisms	PUBMED	Case-control/ 293 subjects,	Thailand	rs3804099; rs3804100.	For the SNP rs3804099, the (C) allele variant was associated with susceptibility to filariasis

Title	Database	Methodology/ Population Size	Country	SNP	Results
and asymptomatic bancroftian filariasis [28].		including 142 patients and 151 controls.			by *Wuchereria bancrofti*. For the SNP rs3804100, the (C) allele variant was associated with susceptibility to filariasis.
A polymorphism in human TLR2 is associated with increased susceptibility to tuberculous meningitis [29].	PUBMED	Case-control/ 747 subjects, with 358 patients and 389 controls.	Vietnam	rs3804099.	The allele (C) variant was associated with a risk of 3 to 6 times greater for the individual to contract tuberculous meningitis.
Polymorphisms in genes TLR1, 2 and 4 are associated with differential cytokine and chemokine serum production in patients with leprosy [10].	PUBMED	Case-control/ 730 subjects, including 362 patients and 368 controls.	Brazil	rs3804099.	The allele (T) variant was associated with an increased risk of developing leprosy per se.
Relationship between toll-like	PUBMED	Case-control/	Poland	rs121917864;	For the SNP rs121917864, the wild allele (C) was

Title	Database	Methodology/ Population Size	Country	SNP	Results
receptor 2 Arg677Trp and Arg753Gln and toll-like receptor 4 Asp299Gly polymorphisms and cytomegalovirus infection [30].	and Science Direct.	229 subjects, with 151 patients and 78 controls.		rs5743708.	associated with cytomegalovirus infection protection. For the SNP rs5743708, the wild allele (G) was associated with increased susceptibility to infection with cytomegalovirus.
TLR4 896A / G and TLR9 1174G / A polymorphisms are associated with the risk of infectious mononucleosis [31].	PUBMED	Clinical trial/ 289 subjects, including 149 patients and 140 healthy individuals.	Poland	rs121917864; rs5743708.	For the SNP rs121917864, the wild allele (C) was detected more frequently in children and adolescents with infectious mononucleosis than in healthy individuals. For the SNP rs5743708, no significant differences were found in individuals with and without the disease.
An association between single nucleotide polymorphisms within TLR and TREM-1 genes and infective endocarditis [32].	PUBMED, MEDLINE a nd Science Direct.	Case-control/ 410 people, with 110 patients and 300 controls.	Russia	rs3804099; rs5743708.	For the SNP rs3804099, the variant (C) allele was associated with susceptibility to infectious endocarditis. For the SNP rs5743708, the allele (A) variant is related to the disease.

Title	Database	Methodology/ Population Size	Country	SNP	Results
Polymorphisms in TLR2 are associated with increased viral shedding and lesional rate in patients with genital herpes simplex virus Type 2 infection [33].	PUBMED	Cohort study/ 128 HSV-2-seropositive subjects.	USA	rs1898830.	The (G) allele variant was associated with HSV-2 genital herpes simplex virus disease at an increased risk of spreading outbreaks and a higher frequency of lesions caused by it.
Toll-like receptor 2 gene polymorphisms, pulmonary tuberculosis, and natural killer cell counts [34].	PUBMED	Cohort study/ 368 subjects, including 184 patients and 184 controls.	Taiwan	rs4696480; rs1898830; rs3804100.	For the SNP rs4696480, the wild (A) allele grants greater susceptibility to pulmonary tuberculosis. For the SNP rs1898830, the wild (A) allele was related to a higher risk of disease development. In rs3804100, (C), variant was responsible for conferring susceptibility to pulmonary tuberculosis with pleural effusion compared to those who did not have pleural effusion.
Toll-like receptor gene variants	PUBMED	Retrospective	USA	rs1898830.	The (G) allele variant is responsible for the association

Title	Database	Methodology/ Population Size	Country	SNP	Results
associated with bacterial vaginosis among HIV-1 infected adolescents [35].		cohort study/ 159 HIV-1 infected subjects.			with Bacterial Vaginosis by *Gardnerella vaginallis*, in coinfection with chlamydia or gonorrhea.
A tool like a receptor gene variants and bacterial vaginosis among HIV-1 infected and uninfected African women [36].	PUBMED	Cohort study/ 372 subjects.	Cameroon, Djibouti, Eritrea, Ethiopia, Madagascar, Malawi, Mauritius, Mozambique, Kenya, Somalia, Seychelles, Tanzania,	rs3804099.	The (C) wild allele was associated with the protection against bacterial vaginosis by *Gardnerella vagi nallis* among HIV-infected women.

Title	Database	Methodology/ Population Size	Country	SNP	Results
			Uganda		
Toll-like receptor 2 gene polymorphisms associated with aggressive periodontitis in Japanese [37].	PUBMED	Retrospective cohort study/ 228 subjects, including 38 patients and 190 healthy controls.	Japan	rs3804100.	The (T) wild allele was responsible for providing protection against aggressive periodontitis related to *Porphyromonas gingivalis* in a Japanese population.
TLR1, TLR2, and TLR6 gene polymorphisms are associated with increased susceptibility to complicated skin and skin structure infections [38].	PUBMED	Randomized Controlled Trial/ 646 individuals, with 318 patients and 328 controls.	Netherlands, Lebanon, Belarus, Bosnia and Herzegovina, Uganda, Czech Republic, Croati	rs5743704; rs5743708.	For the SNP rs5743704, the wild (C) allele confers higher susceptibility to complicated skin and skin structure infections (cSSSIs), caused by the agents including *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus esquisimilis*, *Escherichia coli*, *Enterobacter cloacae*, *Bacteroides fragilis*, *Acinetoba*

Title	Database	Methodology/ Population Size	Country	SNP	Results
			a, Georgia, Slovakia, Estonia, Hungary, Kosovo, Latvia, Lithuania, Macedonia, Moldova, Montenegrin, Poland, Romania, Russia, Sérvia, Ukraine		*cter baumanii* and in smaller portions by other Gram-positive and Gram-negative bacteria. For the SNP rs5743708, no significant associations were observed.
Polymorphisms in Toll-like receptor 9 influence the clinical course of HIV-1 infection [39].	PUBMED	Cohort study/ 428 individuals.	USA	rs3804099; rs3804100; rs5743708.	No correlations were found.

Title	Database	Methodology/ Population Size	Country	SNP	Results
Polymorphisms in TLR-2 are associated with congenital cytomegalovirus (CMV) infection but not with congenital CMV disease [40].	PUBMED	Case-control/ 87 individuals.	Japan	rs1898830; rs3804100.	For the SNP rs1898830, the AG genotype tended to be identified less frequently in children with congenital CMV infection, which indicates protection against the disease. For the SNP rs3804100, the CC genotype was significantly associated with congenital CMV infection, but not with congenital CMV disease.
SNPs in toll-like receptor (TLR) genes as new genetic alterations associated with congenital toxoplasmosis? [41]	PUBMED	Meta-analysis/ 200 cord blood samples obtained from 72 atopic and 128 non-atopic mothers.	Poland	rs4696480; rs1898830.	For the SNP rs4695480, the (A) allele variant was associated with increased expression of Treg marker genes, with GITR (glucocorticoid-induced tumor necrosis factor receptor) and LAG3 (lymphocyte activation gene receptor 3), and also with secretion of cytokines TH2 and TNF-α in case of maternal atopy (predisposition to type 1 hypersensitivity of allergic reactions). In contrast, there are decreased Tregs in cases without maternal atopy.

Title	Database	Methodology/ Population Size	Country	SNP	Results
					For the SNP rs1898830, the wild allele (G) was correlated with Treg-marker genes decreasing and increasing with no maternal atopic disease. It demonstrated the associations of these SNPs with early, but not late, onset of pre-eclampsia.
Correlation between TLR2, TLR3, TLR4, and TLR9 polymorphisms and susceptibility to and prognosis of severe hepatitis among the newborns [42].	PUBMED	Cohort study/ 275 subjects, including 135 patients and 140 controls.	China	rs1898830; rs3804100; rs5743708.	For the SNP rs1898830, the allele (G) variant was associated with a lower risk of severe hepatitis in newborns. For the SNP rs3804100, the allele (C) variant showed a higher correlation with severe hepatitis. For the SNP rs5743708 no significant associations were found between the SNP and disease risk.
Genetic polymorphisms in Toll-like receptors among pediatric patients	PUBMED	Comparative study/ 564	Taiwan	rs3804099; rs3804100;	For the SNP rs3804099, the allele (T) variant was associated with the susceptibility of APN (acute

Title	Database	Methodology/ Population Size	Country	SNP	Results
with renal parenchymal infections of different clinical severities [43].		pediatric patients.			pyelonephritis) and ALN (acute lobar nephronia). For the SNP rs3804100, the wild allele (T) was associated with susceptibility of APN and ALN.
Polymorphisms in toll-like receptors 2, 4 and 5 are associated with Legionella pneumophila infection [44].	PUBMED	Cohort study/ 54 individuals.	China	rs3804099.	The (T) variant allele provided higher protection against infection by *Legionella pneumophila,* with the level of MyD88 mRNA expression (myeloid differentiation protein) significantly lower.
Relationship between toll-like receptor 2 R753Q and T16934A polymorphisms and Staphylococcus aureus nasal carriage [45].	PUBMED	Prospective cohort study/ 299 patients.	Poland	rs5743708; rs4696480.	For the SNP rs5743708, the wild-type (G) allele was responsible for granting susceptibility to infection. For the SNP rs4696480 no correlations were observed.
Gene polymorphisms in pattern	PUBMED	Cohort study/	USA,	rs5743704.	The mutated allele (C) provided higher susceptibility

Title	Database	Methodology/ Population Size	Country	SNP	Results
recognition receptors and susceptibility to idiopathic recurrent vulvovaginal candidiasis [46].		382 subjects, including 119 patients and 263 controls.	Netherlands and France		to recurrent vulvovaginal candidiasis (RVVC).
The association analysis of TLR2 and TLR4 gene with tuberculosis in the Tibetan Chinese population [47].	PUBMED	Cohort study/ 971 subjects, with 467 patients and 504 healthy individuals.	China	rs7696323.	The (T) allele variant was associated with an increased risk of tuberculosis infection.
Association between toll-like receptor2 Arg677Trp and 597T / C gene polymorphisms and pulmonary tuberculosis in Zahedan,	PUBMED and Science Direct.	Case-control/ 351 subjects, including 174 patients and 177	Iran	rs3804099.	The allele (C) variant was associated to be a risk factor for pulmonary tuberculosis.

Title	Database	Methodology/ Population Size	Country	SNP	Results
Southeast Iran [48].		controls.			
Association of SLC11A1 with tuberculosis interactions with NOS2A and TLR2 in African-Americans and Caucasians [49].	PUBMED	Cohort study/ 855 individuals.	USA and Argentina	rs1816702.	The wild allele (T) was associated with an increased risk of tuberculosis infection.
Relationship between Toll-like receptor 2 polymorphism and cytomegalovirus disease after liver transplantation [50].	PUBMED.	Cohort study/ 92 patients.	USA	rs5743708.	The allele (A) variant was associated with cytomegalovirus disease after liver transplantation.
Association between toll-like receptor polymorphisms and the outcome of liver transplantation for chronic hepatitis C virus [51].	PUBMED.	Cohort study/ 92 patients.	USA	rs5743708.	The allele (A) variant was associated with allograft failure and mortality after liver transplantation in chronic HCV.

4. DISCUSSION

The pro-inflammatory response induced by TLRs is considered the host's first defense line and, as well as responsible for the development of innate and adaptive immunity and accelerating the healing process for immune homeostasis restauration [52].

Thus, the manifestation of infectious diseases may be related to alterations in the TLR2 gene expression due to the presence/absence of specific SNPs in the gene, in addition to interactions between genetic, epigenetic and environmental factors. A total of 32 published studies investigating the association of SNPs in TLR2 gene associated with infectious diseases were analyzed, being observed that most of these studies were from USA (21.87%).

The SNPs associated with infectious diseases were rs121917864, rs5743708, rs1816702, rs3804099; rs3804100; rs1898830; rs5743704; rs5743708, rs4696480; rs121917864; rs7696323.

The SNP rs121917864 represents a *missense* mutation, where the amino acid arginine (Arg) is replaced by tryptophan (Trp) at residue 677(Arg677Trp). This mutation affects a conserved arginine residue located near the locus corresponding to the Pro681His mutation, which prevents the interaction with the MyD88 protein necessary for the intracellular signaling, resulting in a reduced pro-inflammatory response. Furthermore, this SNP may affect the TLR2 homodimer and/or the TLR2/TLR1 heterodimer involved in immune response to the 19 kDa lipoprotein of *M. leprae*. This lipoprotein amino acid sequence shares a 47% similarity with the 19 kDa lipoprotein of *M. tuberculosis*, which may justify this SNP relationship with susceptibility to leprosy and tuberculosis [21,22].

The SNP rs5743708 is described as a replacement of guanine (G) by adenine (A) at nucleotide 2258, also being a *missense* mutation that results in a replacement of arginine (Arg) by a glutamine (Gln) at the residue 753. TLR2 presents a C-terminus and probably affects the molecule's signaling function rather than its binding, which are necessary for generation of intracellular signalizing molecules, such as MyD88. Several studies revealed that human cells expressing the TLR2 Arg753Gln polymorphism significantly reduced the degree of nuclear factor-κB (NF-kB) activation, cytokine secretion in response to stimulation by lipoteichoic acid, or other TLR2 ligands compared to wild-type TLR2 SNP [26,51,53]. This SNP was the most reported (13 studies - 40.62%), being firstly described by Lorenz et al. (2000) among 3% of the study population [23].

In the present study, the SNP rs5743708 was related to protection against Lyme disease [26] and susceptibility *to* rheumatic fever (caused by Gram-positive bacteria) [27], tuberculosis [24], cytomegalovirus [30,50], chronic hepatitis C [51], endocarditis [25] and infection by *Staphylococcus* [23,45]. No significant associations were found between this SNP and mononucleosis, complicate skin and structured skin infections (cSSSIs), AIDS and neonatal chronic hepatitis [31,38,39,42]. In *Staphylococcus* infection, the SNP rs5743708 was most commonly found related with a susceptibility role, being the 'A' allele variant predominant in a French population by Lorenz et al., 2000, while the wild-type G allele in a study by Żukowski et al., 2017 in a Polish population [23,45].

For the SNP rs3804099, the synonymous mutation did not result in asparagine (Asn) substitution at residue 199, resulting in a decreased macrophage response, lower TLR2 expression with attenuated host immune response [48] and susceptibility to most of the diseases reported in this study: tuberculosis [48], leprosy [10], acute pyelonephritis and acute lobar nephronia [43], infective endocarditis [32], tuberculous meningitis [29] and filariasis [28]. However, two studies described to protection against bacterial vaginosis, caused by *Gardnerella vaginallis* [36] and infection by *Legionella pneumophila* [44]. In leprosy, it was demonstrated that this SNP caused increased expression of pro-inflammatory cytokines, with higher expression of TLR2 [10]. Finally, this SNP was the second mostly reported (8 studies - 25%).

The SNP rs5743704 results in a non-synonymous missense mutation with amino acid substitution from Proline (Pro) to Histidine (His) at residue 631. It has a dominant negative effect on TLR2 signaling, which impairs the cell to produce proper amounts of cytokines [46,54].

For the SNP rs3804100, the synonymous mutation led to no substitution of amino acid serine (Ser) at residue 450. The SNP was predicted to have a functional effect in decreasing the number of exonic splicing enhancing motifs [55]. Nevertheless, its role in the TLR2 function is unclear.

The SNPs rs4696480 (at position 16934), rs1898830 (at position 15607), rs7696323 (at position 153684593) and rs1816702 (at position 153688371) correspond to gene variations in introns causing no amino acid change. In chronic neonatal hepatitis, toxoplasmosis, cytomegalovirus, tuberculosis and herpes simplex virus type 2, the SNP rs1898830 was related to a lower presence of pro-inflammatory cytokines and expression of TLR2, while in bacterial vaginosis caused by *Gardnerella vaginallis*, higher levels of pro-inflammatory cytokines were detected due to increased expression

of TLR2 [33,36]. For the other SNPs, their roles in the TLR2 gene function and in the inflammatory response so far are not clear.

The majority of studies presenting the role of TLR2 SNPs were in association with tuberculosis, which might be particularly explained due to the fact that TLR2 is the main receptor for lipoproteins in mammals, which are derived from a variety of bacteria, such as *M. tuberculosis*. TLR2 is also required for IL-12 induction, where the IL-12-dependent INF-γ pathway plays an important role in cell-mediated immunity, promoting the Th1 response [56–58]. In this study, tuberculosis was related to the SNPs: rs1816702 (allele (T), wild) [49], rs3804099 (allele (C), variant) [48], rs7696323 (allele (T), variant) [47], rs4696480 (allele (A), wild) [34], rs1898830 (allele (A), wild) [34], rs3804100 (the variant (C) allele) [34] and rs5743708 (the (A) allele, variant) [24].

Since SNPs in the TLR2 gene may be related with susceptibility or protection to pathogenic infections, it is possible that a more comprehensive understanding of this mutation will soon be interpreted as a preventive tool in medicine. The analysis of genetic factors can become an useful strategy to identify individuals at increased risk of specific infections, patients at higher risk of poor disease progression, and contribute to a more effective therapeutic interventions [59].

5. CONCLUSION

To date, several studies reporting the association of TLR2 SNPs with the pathophysiology of specific clinical conditions have been published. There are controversial data in relation to some infectious diseases, which makes it necessary to perform more comprehensive association studies to assess the clinical importance of these SNPs among different populations. The data presented are relevant for future clinical studies examining the importance of SNPs in the TLR genes, also aiding on development of new strategies in clinical diagnosis, treatment and prevention of infectious diseases.

COMPETING INTERESTS

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.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. MJAS was responsible for the conceptualization, formal analysis, investigation, methodology, validation, visualization, writing, drafting and editing. MBML performed the supervision, validation, visualization, writing, reviewing and editing. KVBL performed the supervision, validation, visualization, writing, reviewing and editing. LNGCL managed the conceptualization, investigation, methodology, project administration, supervision, visualization, writing, reviewing and editing. All authors read and approved the final manuscript.

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