Systematic Review

The Relationship of TLR2 Polymorphisms with Infectious Diseases

ABSTRACT

The proinflammatory response induced by Toll-Like receptors (TLR) is considered the host's first line of defense. SNPs correspond to the most frequent type of variation in the human genome and due to the great importance of TLR2 in the immune response, SNPs in the TLR gene are related to sensitivity or resistance to various diseases. Thus, the objective of the research was to identify the polymorphisms existing in the TLR2 gene that cause susceptibility or protection to infectious diseases. This was a systematic review of the literature, carried out in the data bases 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) with cases, comparative, cohort studies, clinical trials, systematic reviews, meta-analyzes between 2000 to 2020. The search resulted in 32 articles, all of which in English, the key points emerging: toll-like receptors and activation and regulation of the immune response; TLR2 and infectious diseases. Thus, it was found that the related polymorphisms are extremely important for the identification of related pathologies, whether for the susceptibility or protection of the individual to the disease and are essential for the mechanisms of signal generation and immune responses so that there must be 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 death in the world and the main cause of years of life adjusted to global disability (1 year of life adjusted to disability is equivalent to 1 year of healthy loss of 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, there has been a recurrence of infectious diseases already eradicated and the emergence of other unknown infectious diseases [2].

In a population endemic for a given disease, some people are diagnosed with active infection, which may or may not be fatal for them, while others are asymptomatic [3]. One reason for these differences is differential immune responses that may be due to variation in the individual's genetic makeup, leading to an ineffective or successful response during infection. A series of studies in the past 50 years have demonstrated the great importance of host immunogenetics in susceptibility and resistance to infections [3–5].

Toll-Like receptors (TLR) are highly conserved transmembrane proteins, which were originally discovered in the 1990s, in insects of the Drosophila genus, being 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. As of this date, ten human Toll receptors have been identified and classified (TLR1-10), each with different specific functions for a specific microbial component [6–8].

The TLRs work like pattern recognition receptors (PRR) present on macrophages, dendritic cells and neutrophils (polymorphonuclear leukocytes or PMN), responsible for recognizing the molecular patterns associated with pathogens (PAMP), which are 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 in that they form 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 lipoteic acid. The TLR2-TLR6 association is responsible for the recognition of lipoteicoic acid from the wall of 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 any PAMP is recognized by the TLR, it promotes phosphorylation of the IκB and its degradation results in the nuclear transcription factor (NF-κB) that will be translocated to the nucleus to induce the expression of inflammatory cytokines and adhesion molecules. The presence of a 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 can result in great susceptibility to pathogens, while hyperactivity is associated with autoimmune diseases, with the unregulated activation of the nuclear factor (NF-kB) being one of the main contributors to the development of cancer [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 result in altering the binding affinity between promoter regions and transcription factors, modifying splicing sites or causing the exchange of an amino acid, leading to variations in the structure and / or function of the protein [12].

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

Hence, due to the great importance of TLR2 in the immune response, SNPs in the TLR gene are related to sensitivity or resistance to various diseases [15,16]. And, in this context, the following research question emerged: Which SNPs exist in the TLR2 gene that cause susceptibility or protection to infectious diseases?

2. METHODOLOGY

This is a systematic bibliographic search, which aims to describe in a theoretical and conceptual way the correlations between polymorphisms of the TLR2 gene and infectious diseases published in the literature. The purpose of such a study adds to the scientific discussion, since the scientific knowledge and bases evaluated and synthesized that constitute relevant evidence can be used as references for new studies.

The study followed the stages of formation: 1- Elaboration of the research question and problem; 2- Stipulation of inclusion and exclusion criteria; 3- Choice of the sample; 4- Analysis of articles; 5- Interpretation, discussion and presentation of the review [17].

To elaborate the research question, the PICO strategy was used, related to the anagram: population; intervention; Comparation; and outcome, as this generates greater integration of results and resolution of the highlighted problem [18].

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

Thus, the research question was carried out, through which the keywords were selected: “TLR2” and “Polymorphisms” and “Infectious Diseases”, together with the Boolean operator “AND”. The research took place 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 were defined as 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-analyzes. The exclusion criteria were articles published prior to the year 2000, articles that were available only in the abstract, letters to the editor and articles with topics not relevant to the research question. Was used for the search display in databases PRISMA flowchart tool that is part of the PRISMA protocol, to show how it reached the final sample, describing all the steps, inclusions and exclusions [19,20].

In the extraction of data, a form consisting of the variables was developed: title, database, methodology, country of study population, SNP and results.

3. RESULTS

Through the application of the inclusion criteria, a total of 67 articles were obtained, however, with the selection of the materials, 35 were excluded, due to duplicity, and some articles were 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). The sample surveys were mostly international (31) and some national (1) derived from Science Direct, MEDLINE and PUBMED.

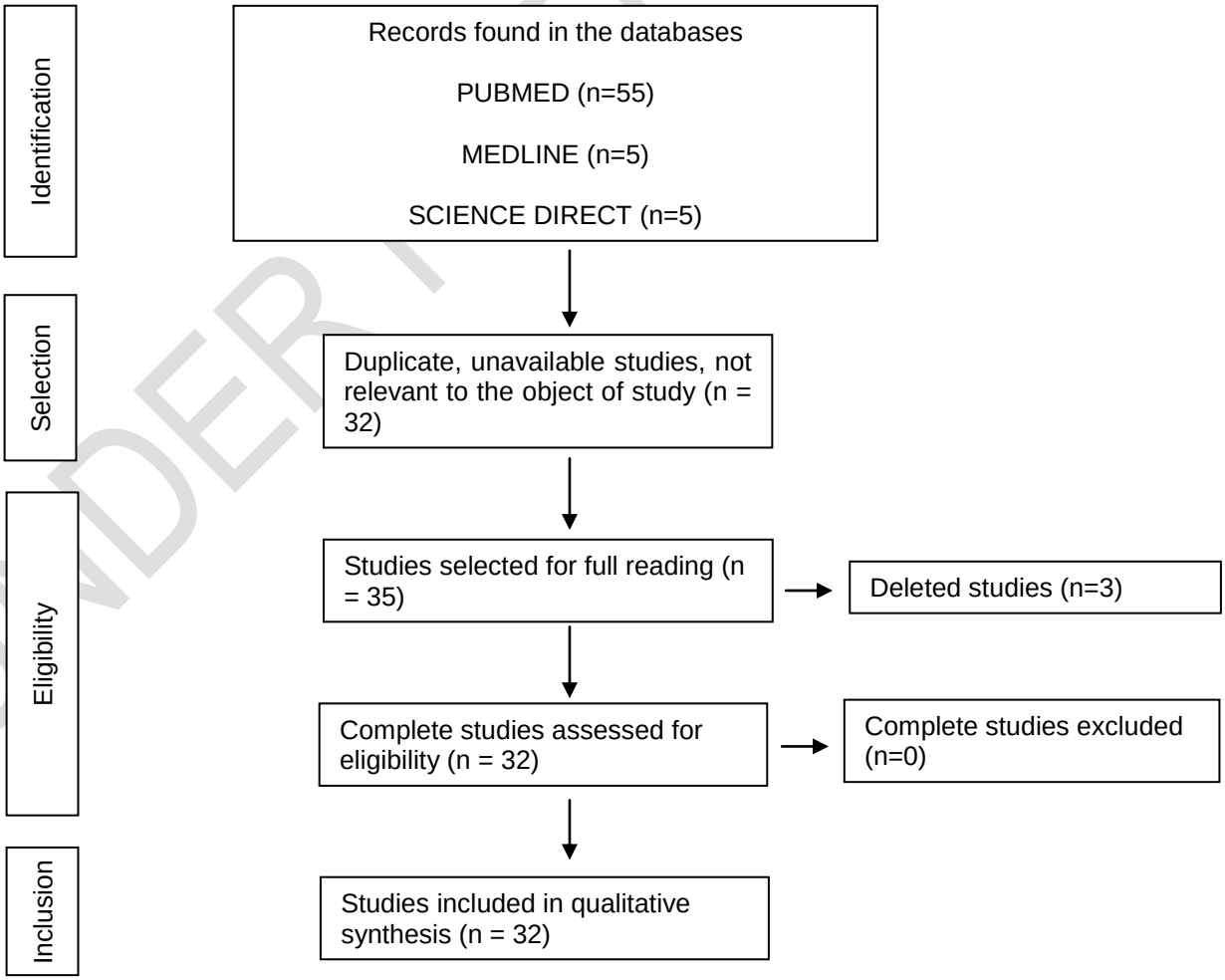

Fig. 1. Flowchart on the procedure for selecting studies, identification and eligibility for analysis. Belém, PA, Brazil, 2020.

Table 1. Synthesis studies by item name, database, study population country, SNP.

Title	Database	Methodology	Study Population Country	SNP	Results
Toll like receptor 2 Arg677Trp polymorphism is associated with susceptibility to tuberculosis in Tunisian patients [21].	PUBMED	Comparative study	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	South Korea	rs121917864; rs5743704.	For SNP rs121817864, the allele (T), variant was associated with leprosy per se and leprosy Lepromatous. For the SNP rs5743704, the (T) allele, variant, was associated with susceptibility to Virchowian leprosy.
A Novel Polymorphism in the Toll-Like Receptor 2 Gene and Its Potential Association with Staphylococcal Infection [23].	PUBMED	Case-control	France.	rs5743708.	The allele (A), variant was associated with susceptibility to septic shock by Staphylococcus infection.
The Arg753GLn polymorphism of	PUBMED	Case-control,	Turkey.	rs5743708.	The (A) variant allele was associated with susceptibility to

Title	Database	Methodology	Study Population Country	SNP	Results
the human Toll-like receptor 2 gene in tuberculosis disease [24].		retrospective			tuberculosis.
Toll-like receptor 2 R753Q polymorphisms are associated with an increased risk of infective endocarditis [25].	PUBMED	Case-control	Spain.	rs5743708.	The allele (A), variant was associated with an increased risk of infective endocarditis.
Heterozygous Arg753Gln polymorphism of human TLR-2 impairs immune activation by Borrelia burgdorferi and protects from late stage Lyme disease [26].	PUBMED	Case-control	Germany.	rs5743708.	The (A) allele, variant was associated with protection against Lyme disease.
TLR-2 gene Arg753Gln polymorphism is strongly associated with acute rheumatic	MEDLINE	Case-control	Turkey.	rs5743708.	The (A) variant allele was associated with rheumatic fever in children caused by Gram-positive bacteria (β-hemolytic streptococci).

Title	Database	Methodology	Study Population Country	SNP	Results
fever in children [27].					
Association between Toll-like receptor 2 (TLR2) polymorphisms and asymptomatic bancroftian filariasis [28].	PUBMED	Case-control	Thailand.	rs3804099; rs3804100.	For rs3804099, the (C) allele, variant was associated with susceptibility to filariasis by *Wuchereria bancrofti*. For 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	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	Brazil.	rs3804099.	The allele (T), variant was associated with increased risk of developing leprosy per se.

Title	Database	Methodology	Study Population Country	SNP	Results
Relationship between toll-like receptor 2 Arg677Trp and Arg753Gln and toll-like receptor 4 Asp299Gly polymorphisms and cytomegalovirus infection [30].	PUBMED and Science Direct.	Case-control	Poland.	rs121917864; rs5743708.	For rs121917864, the allele (C), wild was associated with cytomegalovirus infection protection. For rs5743708, the allele (G), wild 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	Poland.	rs121917864; rs5743708.	For the SNP rs1219 17864, 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 and Science Direct.	Case-control	Russia.	rs3804099; rs5743708.	In rs3804099, the variant (C) allele is associated with susceptibility to infectious endocarditis. In rs5743708, the allele (A), variant is related to the disease.

Title	Database	Methodology	Study Population 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	United States.	rs1898830.	The (G) allele variant is 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	Taiwan.	rs4696480; rs1898830; rs3804100.	For rs4696480, the wild-type (A) allele grants greater susceptibility to pulmonary tuberculosis. For rs1898830, the wild (A) allele allowed a greater risk of developing the disease. In rs3804100, being (C), variant 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	United States.	rs1898830.	The (G) allele, variant is responsible for the association

Title	Database	Methodology	Study Population Country	SNP	Results
associated with bacterial vaginosis among HIV-1 infected adolescents [35].		cohort study			with Bacterial Vaginosis generated by *Gardnerella vaginallis* by the Amsel criteria, in coinfection with chlamydia or gonorrhea.
Tool like receptor gene variants and bacterial vaginosis among HIV-1 infected and uninfected African women [36].	PUBMED	Cohort study	Comoros, Djibo uti, Eritrea, Ethiopia, Madagascar, Malawi, Mauritius, Mozambique, Kenya, Somalia, Seychelles, Tanzania,	rs3804099.	The (C), wild allele was associated with the protection of Bacterial Vaginosis by *Gardnerella vaginallis* in HIV-infected women, as classified by the Nugent criteria.

Title	Database	Methodology	Study Population Country	SNP	Results
			Uganda.		
Toll-like receptor 2 gene polymorphisms associated with aggressive periodontitis in Japanese [37].	PUBMED	Retrospective cohort study	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	Netherlands, Lebanon, Belarus, Bosnia and Herzegovina, Ugandan Republic, Czech Republic, Croatia, Georgia, Slovakia, Estonia, H	rs5743704; rs5743708.	For rs5743704, the wild (C) allele confers greater susceptibility to complicated skin and skin structure infections (cSSSIs), caused by the agents *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus esquisimilis*, *Escherichia coli*, *Enterobacter cloacae*, *Bacteroides fragilis*, *Acinetobacter baumanii* and in smaller *portions* of other Gram-positive and Gram-negative bacteria.

Title	Database	Methodology	Study Population Country	SNP	Results
			ungary, Kosovo, Latvia, Lithuania, Macedonia, Moldova, Montenegrin, Poland, Romania, Russia, Sérvia, Ukraine.		For rs5743708, no significant associations were observed.
Polymorphisms in Toll-like receptor 9 influence the clinical course of HIV-1 infection [39].	PUBMED	Cohort study	United States.	rs3804099; rs3804100; rs5743708.	No correlations were found.
Polymorphisms in TLR-2 are associated with congenital	PUBMED	Case-control	Japan.	rs1898830; rs3804100.	For rs1898830, the AG genotype tended to be identified less frequently in children with congenital CMV infection,

Title	Database	Methodology	Study Population Country	SNP	Results
cytomegalovirus (CMV) infection but not with congenital CMV disease [40].					which indicates protection against the disease. For 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	Poland.	rs4696480; rs1898830.	For rs4695480, the (A) allele, variant was associated with increased expression of the 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. For rs1898830, allele (G), wild correlated with marker genes Treg decreasing and increasing with no maternal

Title	Database	Methodology	Study Population Country	SNP	Results
					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	China.	rs1898830; rs3804100; rs5743708.	For rs1898830, the allele (G) variant possessed a lower risk of severe hepatitis in newborns. For the rs3804100, the allele (C), variant, showed a higher correlation with severe hepatitis. For rs5743708 no significant associations were found between the SNP and the risk of the disease.
Genetic polymorphisms in Toll-like receptors among pediatric patients with renal parenchymal infections of different clinical severities [43].	PUBMED	Comparative study	Taiwan.	rs3804099; rs3804100;	In rs3804099, the allele (T), variant was more associated with the susceptibility of APN (acute pyelonephritis) and ALN (acute lobar nephronia). In rs3804100, frequency of the allele (T), wild associated with APN and ALN was observed.

Title	Database	Methodology	Study Population Country	SNP	Results
Polymorphisms in toll-like receptors 2, 4 and 5 are associated with Legionella pneumophila infection [44].	PUBMED	Case-control	China.	rs3804099.	The (T) variant allele provided greater 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	Poland.	rs5743708; rs4696480.	For rs5743708, the wild-type (G) allele is responsible for granting susceptibility to infection. For rs4696480 no correlation was possible between the infection.
Gene polymorphisms in pattern recognition receptors and susceptibility to idiopathic recurrent vulvovaginal candidiasis [46].	PUBMED	Cohort study	United States, Netherlands and France.	rs5743704.	The mutated allele (C) gives greater susceptibility to recurrent vulvovaginal candidiasis (RVVC).

Title	Database	Methodology	Study Population Country	SNP	Results
The association analysis of TLR2 and TLR4 gene with tuberculosis in the Tibetan Chinese population [47].	PUBMED	Cohort study	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, Southeast Iran [48].	PUBMED and Science Direct.	Case- control	Iran.	rs3804099.	The allele (C), variant is associated to be a risk factor for susceptibility to pulmonary tuberculosis.
Association of SLC11A1 with tuberculosis interactions with NOS2A and TLR2 in African-Americans and Caucasians [49].	PUBMED	Cohort study	United States and Argentina.	rs1816702.	The allele (T), wild was associated with increased risk of tuberculosis infection.
Relationship between Toll-like	PUBMED.	Cohort study	United States.	rs5743708.	The allele (A), variant was associated with the

Title	Database	Methodology	Study Population Country	SNP	Results
receptor 2 polymorphism and cytomegalovirus disease after liver transplantation [50].					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	United States.	rs5743708.	The allele (A), variant was associated with allograft failure and mortality after liver transplantation for chronic HCV.

4. DISCUSSION

The pro-inflammatory response induced by TLRs is considered the host's first line of defense and, in addition to being responsible for the development of innate and adaptive immunity, it accelerates the healing process to restore immune homeostasis [52].

Thus, the manifestation of infectious diseases may be related to alterations in the expression of the TLR2 gene due to the presence/absence of specific SNPs in this gene, and to the additive interactions between several genetic, epigenetic and environmental factors. Therefore, 32 studies published in the literature that investigated the association of SNPs in this gene associated with infectious diseases were analyzed, and it was observed that most of these studies were from United States nationalities (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, which is necessary for the generation of intracellular signals, resulting in a reduced pro-inflammatory response. Furthermore, this SNP may affect the association of the TLR2 homodimer and/or the TLR2/TLR1 heterodimer involved in responses to the *M. leprae* 19 kDa lipoprotein. This lipoprotein shares 47% similarity with the amino acid sequence with the 19 kDa lipoprotein of *M. tuberculosis*, which may justify the relationship of this SNP to susceptibility to leprosy and tuberculosis [21,22].

In rs5743708, it is described as a replacement of guanine (G) by adenine (A) at nucleotide 2258, being a *missense* mutation that results in a replacement of Arginine (Arg) by a Glutamine (Gln) at residue 753. The SNP is located at residue 753. TLR2's own C-terminus and probably affects the molecule's signaling function rather than its binding to targets necessary for the generation of intracellular signals, such as MyD88. Studies have shown that human cells expressing the TLR2 Arg753Gln polymorphism significantly reduced the degree of nuclear factor-κB (NF-kB) activation or cytokine secretion in response to stimulation with lipoteichoic acid or other TLR2 ligands compared to wild-type TLR2 SNP [26,51,53]. This SNP was the most found in our research, present in 13 studies (40.62%), being described for the first time by Lorenz et al. (2000) which determined that it occurred in 3% of the study population [23].

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

For rs3804099, the synonymous mutation does not result in amino acid substitution Asparagine (Asn) at residue 199. SNP results in a decreased macrophage response, lower TLR2 expression with attenuated host immune response [48], resulting in a susceptibility to most of the diseases researched 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 were also found in which this SNP was related to protection against Bacterial Vaginosis, caused by *Gardnerella vaginallis* [36] and infection by *Legionella pneumophila* [44]. In leprosy, it was shown that this SNP caused increased expression of pro-inflammatory cytokines, with greater expression of TLR2 [10]. This SNP was the second most found in our research, present in 8 studies (25%).

The rs5743704 SNP 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 causes the cell to produce consistently very low amounts of cytokines [46,54].

For rs3804100, the synonymous mutation is no amino acid substitution 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, non-coding regions, so there is no amino

acid change. In chronic neonatal hepatitis, toxoplasmosis, cytomegalovirus, tuberculosis and herpes simplex virus type 2, rs1898830 is related to a lower presence of pro-inflammatory cytokines and lower expression of TLR2, while in Bacterial Vaginosis caused by *Gardnerella vaginallis*, release may occur of pro-inflammatory cytokines, with 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 most studied disease in the literature in relation to TLR2 SNPs was tuberculosis. This disease was probably chosen for study because TLR2 is the main receptor for lipoproteins in mammals, which are derived from a variety of bacteria, such as *Mycobacterium tuberculosis*. TLR2 is also required for IL-12 induction. It is known that 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 to 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 be used as a useful strategy to identify individuals at increased risk of specific infections, patients at higher risk of worse disease progression, leading to more effective therapeutic interventions [59].

5. CONCLUSION

To date, several studies linking 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 carry out more comprehensive association studies to assess the clinical importance of these SNPs in different populations. The data presented are relevant for future clinical studies that examine the importance of SNPs in the TLR gene, helping to predict new strategies in the clinical diagnosis, treatment and prevention of infectious diseases.

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