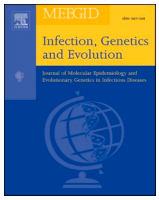
Infection, Genetics and Evolution 93 (2021) 104945

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid



Review

The role of Mannose-binding lectin in leprosy: A systematic review

Rodrigo Feliciano do Carmo [a,*], Jaime Rangel Leal Neves [a], Pablo Rafael Silveira Oliveira [b], Luydson Richardson Silva Vasconcelos [c], Carlos Dornels Freire de Souza [d]

[a] Department of Pharmacy, Federal University of the São Francisco Valley (UNIVASF), Petrolina, Brazil
[b] Biology Institute, Federal University of Bahia (UFBA), Salvador, Brazil
[c] Department of Parasitology, Aggeu Magalhães Institute (IAM), Recife, Brazil
[d] Department of Medicine, Federal University of Alagoas (UFAL), Arapiraca, Brazil

ARTICLE INFO

Keywords:
Complement system
Leprosy
Innate immunity
MBL2
Polymorphism

ABSTRACT

Leprosy is an infectious disease that may present different clinical forms depending on host immune response to *Mycobacterium leprae*. Mannose-binding lectin (MBL) is an acute phase protein associated with the pathophysiology of leprosy. Some studies have shown that there is a correlation between serum levels of MBL and polymorphisms in its gene associated with susceptibility per se and to different clinical forms. The aim of this study was to conduct a systematic review of publications in the literature that studied the association of MBL with leprosy. Databases were searched until December 2020 (PROSPERO: CRD42020158458), and additional searches were conducted scanning the reference lists of the articles. Two independent reviewers assessed the study quality using the Newcastle-Ottawa Quality Assessment Scale. Finally, 10 eligible articles were included in the study. The overall results indicated that both low MBL serum levels and polymorphisms in the structural or promoter region of its gene seem to be associated as protective factors against the development of severe forms. The results suggest that MBL may play a role in the clinical progression of leprosy.

1. Introduction

Leprosy, also known as Hansen's disease, is a chronic infectious disease caused by *Mycobacterium leprae*, a microorganism that has a predilection for the skin and nerves. The damage to peripheral nerves results in sensory and motor impairment with characteristic deformities and disability (Britton and Lockwood, 2004; Bhat and Prakash, 2012). Despite a significant reduction in its global prevalence since the World Health Organization implemented the free multidrug therapy program in 1995, leprosy remains a major cause of morbidity, owing to its associated long-term disabilities and sequelae in an estimated 2 million people worldwide (De Paula et al., 2019; Lockwood and Suneetha, 2005).

Leprosy is characterized by high infectivity and low pathogenicity, since only a small proportion of infected people develop signs of the disease (Scollard et al., 2006). The clinical forms of leprosy are distributed along a spectrum that is associated with host immune alterations, where the predominance of the cellular response (Th1) is related to the tuberculoid clinical form, while the antibody-mediated immune response (Th2) is related to the lepromatous clinical form (de Fonseca et al., 2017). Predisposition to leprosy per se and to progression to different clinical forms may be modulated by several factors, which include early components of the immune response involved in the interaction of *M. leprae* with target cells (Dornelles et al., 2006). There is strong evidence that the development of the disease is under tight human genetic control, where single nucleotide polymorphisms (SNPs) in genes of immunity are good candidates for disease prediction (Gaschignard et al., 2016).

Mannose-binding lectin (MBL) is a soluble protein of innate immunity that plays a key role in pathogen recognition and elimination (Ip et al., 2009). MBL also acts in the acute inflammatory phase, working in the recognition of pathogen receptors. It binds to a wide variety of pathogen surface sugars and plays an important role in innate immunity due to its ability to opsonize pathogens, enhancing phagocytosis and activating the complement cascade via the lectin pathway (Dommett et al., 2006; Ip et al., 2009).

Abbreviations: MBL, mannose-binding lectin; MB, multibacillary; NOS, Newcastle-Ottawa Quality Assessment Scale; OR, odds ratio; PB, paucibacillary; SNPs, single nucleotide polymorphisms.

* Corresponding author at: Universidade Federal do Vale do São Francisco, Av. José de Sá Maniçoba, s/n, Centro, Petrolina-PE, Brazil.
E-mail address: rodrigo.carmo@univasf.edu.br (R.F. do Carmo).

https://doi.org/10.1016/j.meegid.2021.104945
Received 7 April 2021; Received in revised form 22 May 2021; Accepted 26 May 2021
Available online 27 May 2021

The *MBL2* gene is located on chromosome 10, and it comprises 4 exons. Three SNPs in exon 1 significantly alter serum MBL concentrations, with variant alleles resulting from mutations in codons 52 (allele D, Arg52Cys), 54 (allele B, Gly54Asp), and 57 (allele C, Gly57Glu). The wild type is called the "A" allele, while structural variants B, C, and D are often grouped together and referred to as the "O" allele. All 3 mutations occur within the collagen domain, changing MBL's ability to oligomerize and reducing its half-life. The lower-order oligomers affect the binding of MBL to mannan and subsequently result in reduced complement activation due to reduced interaction with the MBL-associated serine proteases (Dommett et al., 2006; Garred et al., 2003; Madsen et al., 1994).

In addition, 3 major SNPs (called "H/L", "Y/X", and "P/Q") in the promoter region are responsible for additional effects on circulating MBL concentration (Madsen et al., 1995). A linkage disequilibrium has been observed among the polymorphisms attributed to the promoter region and structural variants of exon 1, resulting in the 7 most commonly described haplotypes (HYPA, LYPA, LXPA, LYQA, HYPD, LYPB, and LYQC) and, accordingly, 28 conceivable diplotypes (Sunil Singh et al., 2016).

There is increasing evidence suggesting that *MBL2* polymorphisms and MBL serum levels are associated with leprosy susceptibility or development of different clinical forms. The results, however, are inconsistent (Gaschignard et al., 2016; Misch et al., 2010). Thus, considering the important role that MBL plays in immunity against infectious diseases, as well as the evidence suggesting that MBL may influence leprosy clinical course or susceptibility, the aim of this study was to conduct a systematic review to discuss the role of MBL in leprosy.

2. Material and methods

2.1. Search strategy

The systematic review protocol was registered at Prospective Register of Systematic Reviews (PROSPERO) under protocol CRD42020158458. A systematic search was conducted on November 2019 and updated on December 2020 in the following databases: Pubmed (1950–2020), Web of Science (1945–2020), Scopus (1960–2020), and LILACS (1985–2020).

The search terms were based on a combination of the following keywords: leprosy, hansen disease, mbl, mbl2, mannose-binding lectin, mannan-binding lectin. The search strategy used was [(leprosy OR "hansen disease") AND (mbl OR mbl2 OR "mannose-binding lectin" OR "mannan-binding lectin")]. The full search strategy can be found in the Supplementary data (Table S1). The language was restricted to English or Portuguese. The references of all the resulting articles were reviewed to avoid missing other relevant publications.

2.2. Eligibility criteria

The PICOS (Population, Intervention, Comparison, Outcome, and Study Design) framework was used to define the eligibility criteria for the review (Richardson et al., 1995).

We considered all published case-control or cohort studies that evaluated the relationship of MBL serum levels or *MBL2* polymorphisms with leprosy.

Studies were excluded if they were conducted in animals; were written in languages other than English or Portuguese; or were book chapters, review papers, abstracts of communications on meetings, letters to the editor, commentaries to articles, unpublished work, or study protocols. In the event of partially overlapping publications, the study with the highest number of individuals was included in the analysis.

2.3. Quality assessment

The level of bias was assessed for each study using the Newcastle-Ottawa Quality Assessment Scale (NOS) (*Ottawa Hospital Research Institute [WWW Document],* 2000). The NOS consists of the following 3 major components: selection of the study population, comparability, and assessment of exposure. The quality score is calculated by summing the scores of the components. The scores range from 0 to 9. Two reviewers assessed the quality of studies independently. Disagreements were solved consulting a third reviewer.

2.4. Data collection

First, duplicates were removed, and one author screened the articles by titles and abstracts, according to the previously defined eligibility criteria. Second, the full text of each potentially relevant study was screened for content to decide its inclusion in the review. For each accepted study, the following data were extracted: first author, year of publication, study location, sample size of cases and controls, genotyping method, genotype frequency, polymorphism position, serum MBL levels, and main results. Two independent reviewers further checked the extracted data for accuracy and completeness. Reviewers resolved disagreements by consensus.

2.5. Data analysis

The study quality assessment performed by both reviewers was explored with Cohen's kappa. The value of Cohen's kappa can be interpreted as follows: values ≤ 0 indicate no agreement; 0.01 to 0.20 indicate none to slight agreement; 0.21 to 0.40 indicate fair agreement; 0.41 to 0.60 indicate moderate agreement; 0.61 to 0.80 indicate substantial agreement, and 0.81 to 1.00 indicate almost perfect agreement (Landis and Koch, 1977). Statistical analysis was performed using IBM SPSS Statistics, version 22.0 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Search strategy

Database search identified 105 studies of potential interest. Two articles were manually identified from reference lists. After duplicates removal, 58 articles were analyzed for relevant content. Subsequently, 46 studies were removed after reading the titles and abstracts. The full-text of the remaining 12 potentially relevant articles was assessed, and 2 articles were excluded because they were conference abstracts. A total of 10 articles were included, all published in English (Fig. 1).

3.2. Quality assessment

Articles scored between 3 and 8 in the NOS. The items with the lowest classification were "definition of controls" and "control for important factor or additional factor". The item "non-response rate" did not score for any article. Agreement between both independent reviewers was substantial ($k = 0.74$; 95% CI 0.44–1.00; $p = 0.000$). A third reviewer resolved the disagreements. The final score for each article evaluated is shown in Table 1.

3.3. Study characteristics

Of the 10 articles selected, a total of 3004 patients with leprosy (1161 paucibacillary [PB] and 1819 multibacillary [MB]) and 2438 healthy controls were included.

Evaluation of *MBL2* gene polymorphisms was performed in 7 articles (Cardona-Pemberthy et al., 2018; De Messias-Reason et al., 2007; Fitness et al., 2004; Sapkota et al., 2010; Tiyo et al., 2020; Vasconcelos et al., 2011; Zhang et al., 2013), 2 of which evaluated both *MBL2* polymorphisms and MBL serum levels (Tiyo et al., 2020; Vasconcelos et al., 2011) and 1 of which assessed *MBL2* polymorphisms and MBL expression using a luciferase report assay (Zhang et al., 2013). Only 3

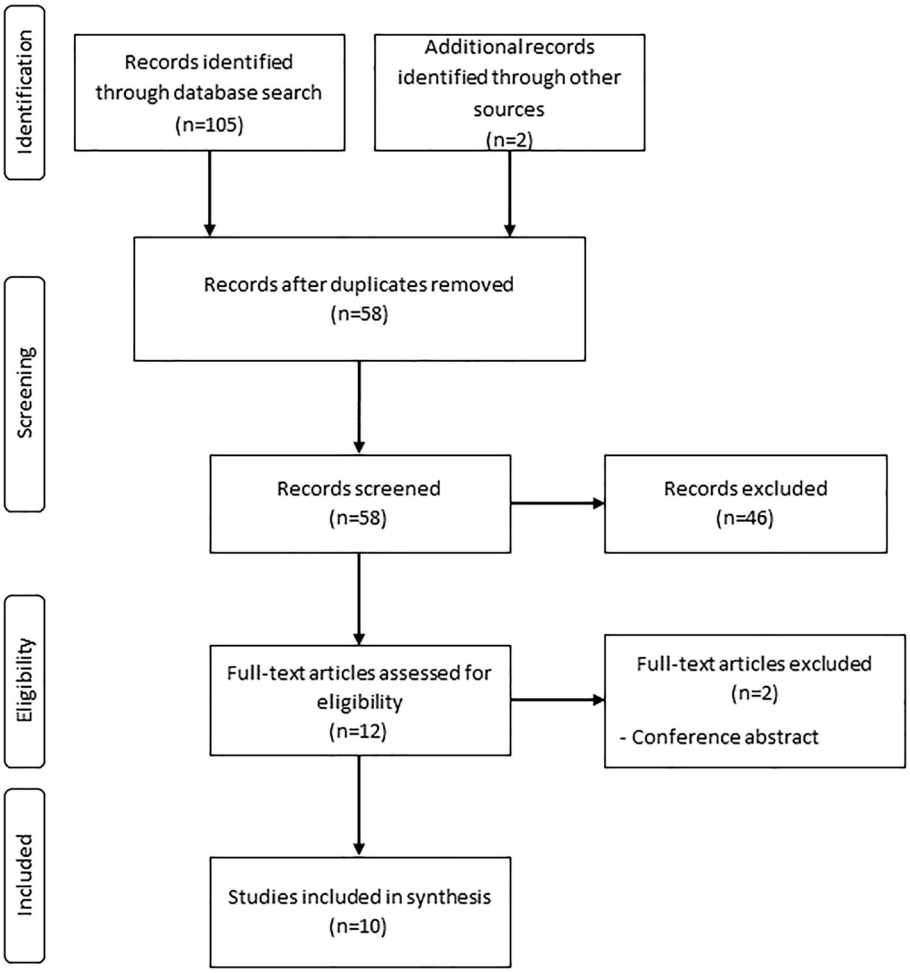


Fig. 1. Flowchart of the study selection process.

Table 1
Quality assessment of included studies using the Newcastle-Ottawa quality assessment scale.

Item/Study	Garred et al., 1994	Fitness et al., 2004	Dornelles et al., 2006	De Messias-Reason et al., 2007	Gomes et al., 2008	Sapkota et al., 2010	Vasconcelos et al., 2011	Zhang et al., 2013	Cardona-Pemberthy et al., 2018	Tiyo et al., 2020
Adequate definition of cases	*	*	*	*	_	*	*	*	*	*
Representativeness of the cases	*	*	*	*	_	*	*	*	*	*
Selection of Controls	*	*	*	*	*	*	*	*	*	*
Definition of Controls	_	*	_	_	_	*	_	*	*	*
Control for important factor or additional factor	_	**	*	*	_	**	_	*	_	**
Exposure assessment	*	*	*	*	*	*	*	*	*	*
Same method of ascertainment for cases and controls	*	*	*	*	*	*	*	*	*	*
Non-Response rate	_	_	_	_	_	_	_	_	_	_
Total Score	5	8	6	6	3	8	5	7	6	8

Note: A study can be awarded a maximum of one star for each item except for the item "Control for important factor or additional factor" which can receive until 2 stars. Quality assessment was performed by two reviewers. Disagreements were solved consulting a third reviewer.

articles analyzed MBL serum levels alone (Dornelles et al., 2006; Garred et al., 1994; Gomes et al., 2008).

The eligible studies included individuals from Ethiopia (Addis Ababa) (Garred et al., 1994), Malawi (Karonga district) (Fitness et al., 2004), Brazil (the states of Pernambuco, Paraná, and Rio de Janeiro) (De Messias-Reason et al., 2007; Dornelles et al., 2006; Gomes et al., 2008; Tiyo et al., 2020; Vasconcelos et al., 2011), Colombia (the states of Bolivar and Antioquia) (Cardona-Pemberthy et al., 2018), China (Yunnan Province) (Zhang et al., 2013), and Nepal (Kathmandu) (Sapkota et al., 2010). A summary of the characteristics of these 7 studies is shown in Table 2.

Table 2
Characteristics of the studies included in the systematic review.

First author's name & Year	Country	Sample size N (PB/MB)	Healthy Controls (N)	Method of MBL assessment	Studied polymorphisms	Main Results
Garred et al., 1994	Ethiopia	36 (0/36)	26	Enzyme immune assay (EIA)	–	Leprosy patients have higher MBL levels than healthy controls.
Fitness et al., 2004	Malawi	270 (244/26)	452	Ligase Detection Reaction (LDR)	Exon 1 (codons 52 (D), 54 (B), and 57 (C))	*MBL2* codons 52 and 54 variants were too rare in this population (minor allele frequency < 1%). No association found between *MBL2* (codon 57) polymorphism and leprosy susceptibility or clinical forms.
Dornelles et al., 2006	Brazil	191 (43/148)	110	ELISA	–	Deficiency of MBL (<100 ng/mL) has a protective effect on lepromatous leprosy. No significant difference in the distribution of MBL levels between patients and controls.
De Messias-Reason et al., 2007	Brazil	264[a] (53/187)	214	Sequencing	Exon 1 (codons 52 (D), 54 (B), and 57 (C)) Promoter: −550 (H/L), −221 (Y/X), +4 (P/Q)	LYPA haplotype increases susceptibility to leprosy per se. Defective haplotypes/genotypes protects against lepromatous and borderline leprosy.
Gomes et al., 2008	Brazil	91 (33/58)	31	ELISA	–	Tuberculoid patients (PB) presented the lowest MBL mean values compared with those with lepromatous and dimorphic forms (MB).
Sapkota et al., 2010	Nepal	933 (352/581)	101	MALDI-TOF mass spectrometry	Exon-1 (codons 52 (D), 54 (B), and 57 (C))	No association was found between *MBL2* polymorphisms and leprosy susceptibility per se. Codon 54 variant, associated with low MBL levels, protects against lepromatous leprosy compared to tuberculoid form.
Vasconcelos et al., 2011	Brazil	228 (67/161)	232	ELISA Real-time PCR	Exon 1 (codons 52 (D), 54 (B), and 57 (C)) Promoter: −550 (H/L), −221 (Y/X)	No association was found between MBL2 gene polymorphisms or serum levels with leprosy susceptibility or clinical forms.
Zhang et al., 2013	China	527 (248/279)	583	Sequencing PCR-RFLP Luciferase Assay	Promoter: −550 (H/L), −221 (Y/X), +4 (P/Q), rs7100749, rs11003124.	Compared with PB patients, *MBL2* haplotypes associated to low transcriptional activity had a protective effect for MB.
Cardona-Pemberthy et al., 2018	Colombia	114 (50/64)	339	PCR-RFLP	Exon 1 (codon 57 (C))	*MBL2* C variant increases the risk for PB leprosy.
Tiyo et al., 2020	Brazil	350 (71/279)	350	ELISA PCR-SSP	Exon-1 (codons 52 (D), 54 (B), and 57 (C))	A/O genotype in women was associated with a susceptibility to leprosy development per se. TGG haplotype[b] was associated with a susceptibility to the development of leprosy per se in women. Patients with B variant were more susceptible to the development of MB leprosy. A/O genotype in women was associated with progression to MB leprosy. CAG haplotype[b] was associated with a susceptibility to the development of MB leprosy in women. No difference was observed between the serum levels of MBL from MB and PB patients.
Total	–	3004 (1161/1819)	2438	–	–	

[a] In 24 patients the clinical form was not determined.
[b] Combination of variants in codons 52 (C > T), 54 (G > A) and 57 (G > A).

4. Discussion

This is the first systematic review to address the role of MBL serum levels and *MBL2* genetic polymorphisms in leprosy. MBL plays an important role in the recognition of microorganisms in the early stage and following steps of the immune response through complement activation and opsonophagocytosis (Turner, 2003).

Strong evidence has shown that MBL could facilitate the ingestion and spread of intracellular pathogens through C3 opsonization (Ambrosio and De Messias-Reason, 2005; De Miranda Santos et al., 2001). In leprosy, this could lead to the development of the most widespread form, namely, lepromatous. The hypothesis that high serum levels of MBL could facilitate the uptake of *M. leprae* by macrophages was proposed for the first time by Garred et al. in 1994 (Garred et al., 1994). They found significantly higher levels of MBL in 36 Ethiopian patients with lepromatous/borderline lepromatous leprosy than in healthy blood donors.

In a study conducted in the South Region of Brazil, no difference was found in the median MBL serum levels between patients with leprosy ($n = 191$) and a control group ($n = 110$), or between the different clinical forms. However, the authors showed that serum MBL deficiency (< 100 ng/mL) was more frequent in patients with the tuberculoid form than in those with the lepromatous form, suggesting a protective role for MBL deficiency against the development of the most severe and MB form of leprosy (Dornelles et al., 2006). This finding is corroborated by another study in the Southeast Region of Brazil, where patients with the tuberculoid form presented lower mean MBL levels than those with the lepromatous or dimorphic forms (Gomes et al., 2008). On the other hand, 2 studies conducted in Brazil's Northeast and Southeast Regions failed to demonstrate any association between MBL serum levels and clinical forms (Tiyo et al., 2020; Vasconcelos et al., 2011).

Although serum MBL levels are influenced by age (Ip et al., 2004; Vasconcelos et al., 2011), we do not believe that this was a confounding factor in the studies described here, because most of them paired by sex and age or controlled for this by multivariate logistic regression (Table 1). On the other hand, MBL serum levels are highly influenced by several polymorphisms in its gene. This could explain the divergent results between studies conducted in different populations. A summary

of the minor allele frequency distribution of the most studied polymorphisms in the *MBL2* gene in different populations is shown in the Supplementary data (Table S2).

Studies investigating the association of *MBL2* polymorphisms with leprosy have shown conflicting results (Cardona-Pemberthy et al., 2018; De Messias-Reason et al., 2007; Fitness et al., 2004; Sapkota et al., 2010; Tiyo et al., 2020; Vasconcelos et al., 2011; Zhang et al., 2013). Fitness et al. (2004) found no association of *MBL2* polymorphisms with PB leprosy in patients from Southeast Africa (Fitness et al., 2004). In line with this, Vasconcelos et al. (2011) also did not find any significant differences in the frequencies of *MBL2* exon 1 and promoter region variants between patients and controls or between clinical forms (Vasconcelos et al., 2011).

In contrast, other studies have found significant association between *MBL2* gene polymorphisms and susceptibility to leprosy per se or clinical forms (Cardona-Pemberthy et al., 2018; De Messias-Reason et al., 2007; Sapkota et al., 2010; Tiyo et al., 2020; Zhang et al., 2013). A study in the South Region of Brazil, investigating the association of *MBL2* polymorphisms at 3 positions in the promoter region (H/L, X/Y, and P/Q) and the variant alleles of the structural region (B, C, and D) in patients with leprosy ($n = 264$) and controls ($n = 214$), showed, for the first time, an association between haplotypes/genotypes of low MBL expression and protection against the development of lepromatous and borderline leprosy (MB). Additionally, the LYPA haplotype, associated with high MBL expression, was associated with susceptibility to leprosy per se and to progression to the lepromatous and borderline forms of the disease (De Messias-Reason et al., 2007). In the same way, Zhang et al. (2013) found that the *MBL2* promoter polymorphisms were strongly associated with leprosy in Han Chinese patients. They showed that, compared with patients with PB leprosy, *MBL2* haplotypes associated with low transcriptional activity had a protective effect against MB (Zhang et al., 2013).

A study with a significant number of patients ($n = 933$) with leprosy from Nepal (Sapkota et al., 2010) evaluated the association of *MBL2* exon 1 polymorphisms (B, C, and D) with leprosy susceptibility, clinical forms, and leprosy reactions. The results showed that the B variant in homozygosity, associated with low MBL levels, was associated with a reduced risk of lepromatous leprosy when compared with tuberculoid leprosy. There was no association between *MBL2* and leprosy susceptibility or leprosy reaction. Accordingly, Cardona-Pemberthy et al. (2018) found that the *MBL2* C variant increased the risk for PB leprosy, signifying a protective role against MB, in Colombian patients (Cardona-Pemberthy et al., 2018).

In contrast with the previous findings, a recent study in the Southeast Region of Brazil showed a significant association of the *MBL2* B variant and the CAG haplotype in exon 1 with susceptibility to the development of MB leprosy. In addition, the A/O genotype and the TGG haplotype were associated with susceptibility to leprosy development per se (Tiyo et al., 2020).

Hypotheses explaining the selective advantage of *MBL2* polymorphisms arose from studies describing a higher frequency of MBL structural gene mutations in some populations. This assumption is supported by a study performed by Garred et al., in 1994, where they showed that about 20% of Eskimos, 40% of Caucasians, and 50% of Africans carried one of the *MBL2* variant alleles (Madsen et al., 1994). In some Indigenous tribes from South America, the frequency of the B allele can reach 42% to 46% (Garred Hans Madsen et al., 1998). Thus, the presence of mutations that confer low levels of MBL can be advantageous in some situations, as has been shown in diseases such as tuberculosis (Cosar et al., 2008) and leishmaniasis (Hamdi et al., 2013).

In summary, the results found in the genetic studies corroborate, at least in part, the hypothesis that MBL may influence the risk of leprosy susceptibility and clinical forms. Discrepancy in the results between the studies may be explained by differences in the frequencies of *MBL2* polymorphisms among the studied populations. This is well evidenced in the study from Malawi (Fitness et al., 2004), where the frequency of variants in codons 52 and 54 were very low. Another explanation would be the difference in the gene regions studied among different studies. Some of them have evaluated only mutations in exon 1 of the *MBL2* gene. However, it is important to highlight that the promoter region exerts great influence on MBL levels and must be taken into consideration.

5. Conclusions

Analysis of the studies included in this systematic review has made it possible to conclude the following:

- *MBL2* variants in exon 1, associated with production of a protein with low oligomerization capacity and, consequently, low functional activity, may act as a protective factor against the development of more severe clinical forms.
- Polymorphisms located in the *MBL2* promoter region, associated with low MBL production levels, have been associated as a protective factor against the development of severe forms of leprosy.
- Further studies are needed to elucidate the role of *MBL2* polymorphisms in the susceptibility to leprosy per se.
- Low serum MBL levels seem to be associated as a protective factor against the development of severe forms of leprosy, but studies are scarce and have conflicting results.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.meegid.2021.104945.

References

Ambrosio, A.R., De Messias-Reason, I.J.T., 2005. Leishmania (Viannia) braziliensis: interaction of mannose-binding lectin with surface glycoconjugates and complement activation. An antibody-independent defence mechanism. Parasite Immunol. 27, 333–340. https://doi.org/10.1111/j.1365-3024.2005.00782.x.

Bhat, R.M., Prakash, C., 2012. Leprosy: an overview of pathophysiology. Interdiscip. Perspect. Infect. Dis. https://doi.org/10.1155/2012/181089.

Britton, W.J., Lockwood, D.N.J., 2004. Leprosy. Lancet 1209–1219. https://doi.org/10.1016/S0140-6736(04)15952-7.

Cardona-Pemberthy, V., Rendón, M., Beltrán, J.C., Soto-Ospina, A., Muñoz-Gomez, A., Araque-Marín, P., Corredor, M., Bedoya, G., Cardona-Castro, N., 2018. Genetic variants, structural, and functional changes of myelin protein zero and mannose-binding lectin 2 protein involved in immune response and its allelic transmission in families of patients with leprosy in Colombia. Infect. Genet. Evol. 61, 215–223. https://doi.org/10.1016/j.meegid.2018.04.002.

Cosar, H., Ozkinay, F., Onay, H., Bayram, N., Bakiler, A.R., Anıl, M., Can, D., Özkınay, C., 2008. Low levels of mannose-binding lectin confers protection against tuberculosis in Turkish children. Eur. J. Clin. Microbiol. Infect. Dis. 27, 1165–1169. https://doi.org/10.1007/s10096-008-0573-8.

de Fonseca, A.B.L., do Simon, M.V., Cazzaniga, R.A., de Moura, T.R., de Almeida, R.P., Duthie, M.S., Reed, S.G., de Jesus, A.R., 2017. The influence of innate and adaptative immune responses on the differential clinical outcomes of leprosy. Infect. Dis. Poverty. https://doi.org/10.1186/s40249-016-0229-3.

De Messias-Reason, I.J., Boldt, A.B.W., Braga, A.C.M., Stahlke, E.V.R.S., Dornelles, L., Pereira-Ferrari, L., Kremsner, P.G., Kun, J.F.J., 2007. The association between mannan-binding lectin gene polymorphism and clinical leprosy: new insight into an old paradigm. J. Infect. Dis. 196, 1379–1385. https://doi.org/10.1086/521627.

De Miranda Santos, I.K.F., Costa, C.H.N., Krieger, H., Feitosa, M.F., Zurakowski, D., Fardin, B., Gomes, R.B.B., Weiner, D.L., Harn, D.A., Ezekowitz, R.A.B., Epstein, J.E., 2001. Mannan-binding lectin enhances susceptibility to visceral leishmaniasis. Infect. Immun. 69, 5212–5215. https://doi.org/10.1128/IAI.69.8.5212-5215.2001.

De Paula, H.L., De Souza, C.D.F., Silva, S.R., Martins-Filho, P.R.S., Barreto, J.G., Gurgel, R.Q., Cuevas, L.E., Santos, V.S., 2019. Risk factors for physical disability in patients with leprosy: a systematic review and meta-analysis. JAMA Dermatol. 155, 1120–1128. https://doi.org/10.1001/jamadermatol.2019.1768.

Dommett, R.M., Klein, N., Turner, M.W., 2006. Mannose-binding lectin in innate immunity: past, present and future. Tissue Antigens 68, 193–209. https://doi.org/10.1111/j.1399-0039.2006.00649.x.

Dornelles, L.N., Pereira-Ferrari, L., Messias-Reason, I., 2006. Mannan-binding lectin plasma levels in leprosy: deficiency confers protection against the lepromatous but not the tuberculoid forms. Clin. Exp. Immunol. 145, 463–468. https://doi.org/10.1111/j.1365-2249.2006.03161.x.

Fitness, J., Floyd, S., Warndorff, D.K., Crampin, A.C., Fine, P.E.M., Hill, A.V.S., 2004. Large-Scale Candidate Gene Study of Leprosy Susceptibility in the Karonga District of Northern Malawi.

Garred Hans Madsen, P.O., Leonardo Satz, M., Hogh, B., 1998. America Populations from Southeast Africa and South Protein Levels of Mannan-Binding Lectin in Different Molecular Events Result in Low.

Garred, P., Harboe, M., Oettinger, T., Koch, C., Svejgaard, A., 1994. Dual role of Mannan-binding protein in infections: another case of heterosis? Int. J. Immunogenet. 21, 125–131. https://doi.org/10.1111/j.1744-313X.1994.tb00183.x.

Garred, P., Larsen, F., Madsen, H.O., Koch, C., 2003. Mannose-binding lectin deficiency - revisited. In: Molecular Immunology. Elsevier Ltd, pp. 73–84. https://doi.org/10.1016/S0161-5890(03)00104-4.

Gaschignard, J., Grant, A.V., Van Thuc, N., Orlova, M., Cobat, A., Huong, N.T., Ba, N.N., Thai, V.H., Abel, L., Schurr, E., Alcaïs, A., 2016. Pauci- and multibacillary leprosy: two distinct, genetically neglected diseases. PLoS Negl. Trop. Dis. https://doi.org/10.1371/journal.pntd.0004345.

Gomes, G.I., Nahn, E.P., Santos, R.K.R.G., Da Silva, W.D., Kipnis, T.L., 2008. The functional state of the complement system in leprosy. Am. J. Trop. Med. Hyg. 78, 605–610. https://doi.org/10.4269/ajtmh.2008.78.605.

Hamdi, S., Ejghal, R., Idrissi, M., Ezzikouri, S., Hida, M., Soong, L., Amarouch, H., Lemrani, M., 2013. A variant in the promoter of MBL2 is associated with protection against visceral leishmaniasis in Morocco. Infect. Genet. Evol. 13, 162–167. https://doi.org/10.1016/j.meegid.2012.09.002.

Ip, W.K., To, Y.F., Cheng, S.K., Lau, Y.L., 2004. Serum mannose-binding lectin levels and mbl2 gene polymorphisms in different age and gender groups of southern Chinese adults. Scand. J. Immunol. 59, 310–314. https://doi.org/10.1111/j.0300-9475.2004.01392.x.

Ip, W.K.E., Takahashi, K., Ezekowitz, R.A., Stuart, L.M., 2009. Mannose-binding lectin and innate immunity. Immunol. Rev. 230, 9–21. https://doi.org/10.1111/j.1600-065X.2009.00789.x.

Landis, J.R., Koch, G.G., 1977. The measurement of observer agreement for categorical data. Biometrics 33, 159. https://doi.org/10.2307/2529310.

Lockwood, D.N.J., Suneetha, S., 2005. Leprosy: too complex a disease for a simple elimination paradigm. Bull. World Health Organ. 83, 230–235 (doi:/S0042-96862005000300018).

Madsen, H.O., Garred, P., Kurtzhals, J.A.L., Lamm, L.U., Ryder, L.P., Thiel, S., Svejgaard, A., 1994. A new frequent allele is the missing link in the structural polymorphism of the human mannan-binding protein. Immunogenetics 40, 37–44. https://doi.org/10.1007/BF00163962.

Madsen, H.O., Garred, P., Thiel, S., Kurtzhals, J.A., Lamm, L.U., Ryder, L.P., Svejgaard, A., 1995. Interplay between promoter and structural gene variants control basal serum level of mannan-binding protein. J. Immunol. 155.

Misch, E.A., Berrington, W.R., Vary, J.C., Hawn, T.R., 2010. Leprosy and the human genome. Microbiol. Mol. Biol. Rev. 74, 589–620. https://doi.org/10.1128/mmbr.00025-10.

Ottawa Hospital Research Institute [WWW Document]. n.d. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 1.9.21).

Richardson, W.S., Wilson, M.C., Nishikawa, J., Hayward, R.S., 1995. The well-built clinical question: a key to evidence-based decisions. ACP J. Club. https://doi.org/10.7326/ACPJC-1995-123-3-A12.

Sapkota, B.R., Macdonald, M., Berrington, W.R., Misch, E.A., Ranjit, C., Siddiqui, M.R., Kaplan, G., Hawn, T.R., 2010. Association of TNF, MBL, and VDR polymorphisms with leprosy phenotypes. Hum. Immunol. 71, 992–998. https://doi.org/10.1016/j.humimm.2010.07.001.

Scollard, D.M., Adams, L.B., Gillis, T.P., Krahenbuhl, J.L., Truman, R.W., Williams, D.L., 2006. The continuing challenges of leprosy. Clin. Microbiol. Rev. https://doi.org/10.1128/CMR.19.2.338-381.2006.

Sunil Singh, S., Chi Fai Cheung, R., Ho Wong, J., Bun Ng, T., 2016. Mannose binding lectin: a potential biomarker for many human diseases. Curr. Med. Chem. 23, 3847–3860. https://doi.org/10.2174/0929867323666160817162208.

Tiyo, B.T., Vendramini, E.C.L., de Souza, V.H., Colli, C.M., Alves, H.V., Sell, A.M., Zucoloto, S.B.P., Visentainer, J.E.L., 2020. Association of MBL2 exon 1 polymorphisms with multibacillary leprosy. Front. Immunol. 11, 1–7. https://doi.org/10.3389/fimmu.2020.01927.

Turner, M., 2003. The role of mannose-binding lectin in health and disease. Mol. Immunol. 40, 423–429. https://doi.org/10.1016/S0161-5890(03)00155-X.

Vasconcelos, L.R.S., Fonseca, J.P.L., do Carmo, R.F., de Mendonça, T.F., Pereira, V.R.A., Lucena-Silva, N., Pereira, L.M.M.B., Moura, P., do de Cavalcanti, M.S.M., 2011. Mannose-binding lectin serum levels in patients with leprosy are influenced by age and MBL2 genotypes. Int. J. Infect. Dis. 15, 551–557. https://doi.org/10.1016/j.ijid.2011.04.008.

Zhang, D.F., Huang, X.Q., Wang, D., Li, Y.Y., Yao, Y.G., 2013. Genetic variants of complement genes ficolin-2, mannose-binding lectin and complement factor h are associated with leprosy in han chinese from Southwest China. Hum. Genet. 132, 629–640. https://doi.org/10.1007/s00439-013-1273-8.