



Association between *MBL2* gene polymorphism and rheumatic fever: a systematic review and meta-analysis

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Background: Mannose-binding lectin 2 gene (*MBL2*) has been reported to play important roles in the pathogenesis of several acute and chronic inflammatory diseases and autoimmune diseases. Rheumatic fever (RF) is the result of autoimmune response of *Streptococcus pyogenes* infection. We conducted a systematic review and meta-analysis to investigate the association between *MBL2* gene polymorphism and RF.

Methods: PubMed, Cochrane Library, Embase, Chinese National Knowledge Infrastructure Database (CNKI), and Web of Science database through June 2021 were searched for studies assessing the association of *MBL2* gene polymorphism in individuals with or without RF. The main outcome included the *MBL2* gene expression. Mantel-Haenszel χ^2 test and the I^2 statistic were used in this meta-analysis. Newcastle-Ottawa Scale was used for quality assessment.

Results: Five studies involving 1,030 patients were included with moderate to high quality. The pooled results showed that there is no association between *MBL2* gene polymorphism and RF: A vs. O: OR: 1.02, 95% CI: 0.52–2.01, $I^2=88%$, $P<0.0001$; AA + AO vs. OO: OR: 1.10, 95% CI: 0.23–5.19, $I^2=84%$, $P<0.0001$; AA vs. AO + OO: OR: 1.03, 95% CI: 0.63–1.59, $I^2=67%$, $P=0.02$; AA vs. OO: OR: 1.11, 95% CI: 0.22–5.69, $I^2=85%$, $P<0.0001$; AA vs. AO: OR: 1.09, 95% CI: 0.82–1.44, $I^2=3%$, $P=0.39$; AO vs. OO: OR: 1.07, 95% CI: 0.27–4.26, $I^2=77%$, $P=0.002$.

Discussion: We found that there is no association between RF and *MBL2*. However, although *MBL2* alleles do contribute to rheumatic etiology, we speculate that patients with RF with B allele may have faster disease progression. Because the limited number of patients and the weak effect of the *MBL2* gene, further studies are needed to verify if *MBL2* genotypes could be a marker for RF and other rheumatic diseases.

Keywords: Mannan-binding lectin; rheumatic fever (RF); complement; meta-analysis

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Introduction

Rheumatic fever (RF) is commonly believed to be a pathological condition resulting from *Streptococcus pyogenes*,

also known as group A streptococcus (1). Recurrences of RF or untreated *Streptococcus pyogenes* may cause further vascular disease, with approximately 50% to 75% of patients

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progressing to rheumatic heart disease (RHD) (2), which causes cardiac morbidity and mortality in disadvantaged populations globally (3,4). According to a global, regional, and national survey from 1990 to 2015, more than 33 million patients were living in *Streptococcus pyogenes* endemic areas (5). Although the mechanism of RF has not been completely clarified, studies believed that RF is an immunity reaction of molecular mimicry between streptococcal antigens, environmental factors such as ultraviolet rays, other human proteins (6) (serum protein electrophoresis showed that albumin decreased, A2 and Y globulin increased, and mucin also increased; immunoglobulin IgM/IgG, complement increased in the acute stage, especially complement C3 and C4 changed on the second day after the clinical symptoms of RF) and genetic factors account for approximately 60% of rheumatoid arthritis (RA) susceptibility (7).

MBL-2, an autosomal gene, is located on chromosome 10q11.2-q21 and consists of four exons (8). rs1800450, rs1800451, and rs5030737 in *MBL2* gene contain 3 different allelic variants [A (wild type), B, C, and D, respectively] and the homozygotes are nonfunctional monomers (9), so the *MBL2* gene variants B, C, and D are often pooled and collectively known as O. The main function of *MBL2* includes Activate complement, promote photoacoustic phagocytosis, regulate inflammation, and promote cell apoptosis (10), so such *MBL2* gene has been shown to be associated with a generalized increased risk of infections. *MBL2* activates the complement system through the lectin pathway (11) and plays a crucial role in innating immune system (12). Many previous studies have demonstrated that the serum levels of MBL is associated with vulvovaginal candidiasis (13), and pulmonary tuberculosis (12). Besides, Ramasawmy *et al.* concluded that defective *MBL2* alleles contribute to rheumatic etiology (14). However, Marzetti *et al.* thought that *MBL2* is not in the pathogenesis and in the clinical manifestations of RF (15). There is no consensus regarding the association between *MBL2* and rheumatism.

To attempt to clarify whether *MBL2* gene plays an important role in RF, therefore, we carried out this study to determine whether the expression of *MBL2* enhances the risk of RF. We present the following article in accordance with the PRISMA reporting checklist (available at <https://jxym.amegroups.com/article/view/10.21037/jxym-21-39/rc>) (16).

Methods

Literature search

We searched medical literature and conducted our study by two independent authors for literature regarding the association between *MBL2* gene polymorphism and RF. English electronic databases such as PubMed, Embase, Cochrane Library, Web of Science and CNKI were used to search the literature from January 1995 to June 2021. Key words used in PubMed were as follows: (“mannose-binding lectin gene” OR “MBL” OR “MBL2”) AND (“rheumatic heart disease” OR “RHD”) AND (“rheumatic fever” or “RF”). Search strategies for other databases were modified if necessary.

Selection criteria

Inclusion criteria: (I) primitive research; (II) one group described subjects were patients with RF; (III) another group described normal subjects (healthy people); (IV) the original data is complete, and the relevant data can be analyzed directly or indirectly; (V) studies reported the proportion of the *MBL2* gene type of included patients.

Exclusion criteria: (I) literature reviews, lectures, cases and letters; (II) the sample size of a single group is less than 15; (III) the original data is incomplete and the relevant data in the literature cannot be extracted.

Data extraction

We extracted author's name, year of publication, study methods, patients' characteristics, and outcomes.

Quality assessment

The methodological quality of non-randomized controlled trials was evaluated according to the recommendations in the Newcastle-Ottawa Scale. The studies scored ≥ 6 were considered to be high quality articles of Newcastle-Ottawa Scale for retrospective studies.

Statistical analysis

Meta-analysis was performed using the Revman 5.3 software provided by Cochrane Collaboration Organization. We

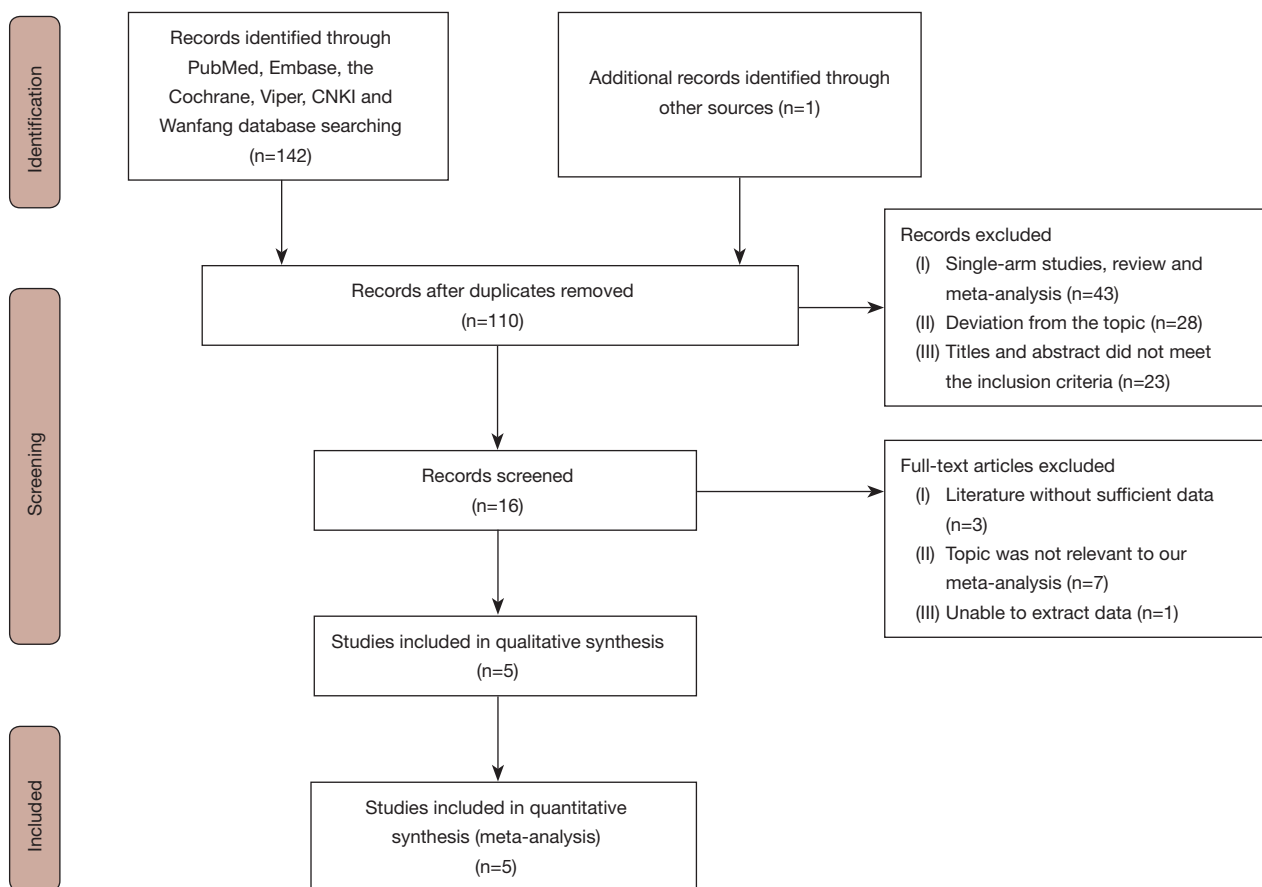


Figure 1 Flowchart of the selection of researches.

calculated the combined odds ratio (OR) of the patient group and the normal human and the 95% confidence interval (95% CI). Heterogeneity will be assessed by Mantel-Haenszel χ^2 test and the I^2 statistic. When $I^2 \leq 50\%$, pooled outcomes and 95% CIs were calculated using Mantel-Haenszel method with fixed-effect models, or a random-effect model will be performed. $P < 0.05$ is statistically significant (two sides).

Results

Literature search and characteristics of the included studies

The detailed literature search is presented in *Figure 1*. The initial search included 143 studies, 33 were removed because of duplicate records, and 94 were excluded after a review of titles/abstracts. Finally, 16 studies were potentially appropriate for further analysis. However, 10 articles were excluded after we read the full text. Eventually, 5

retrospective studies (14,17-20) were included in this meta-analysis (*Table 1*).

All of the included studies were scaled as a total score more than 5 with a low risk of bias.

Findings of meta-analysis

Our results indicated that there is no significant association between *MBL2* gene polymorphism, and the ORs (95% CIs) for the influence of *MBL2* gene polymorphism are detailed in *Figures 2*. There was no statistically difference under pooled results. A vs. O: OR 1.02, 95% CI: 0.52–2.01, $I^2=88\%$, $P < 0.0001$ (*Figure 2A*); AA + AO vs. OO: OR 1.10, 95% CI: 0.23–5.19, $I^2=84\%$, $P < 0.0001$ (*Figure 2B*); AA vs. AO + OO: OR 1.03, 95% CI: 0.63–1.59, $I^2=67\%$, $P=0.02$ (*Figure 2C*); AA vs. OO: OR 1.11, 95% CI: 0.22–5.69, $I^2=85\%$, $P < 0.0001$ (*Figure 2D*); AA vs. AO: OR 1.09, 95% CI: 0.82–1.44, $I^2=3\%$, $P=0.39$ (*Figure 2E*); AO vs. OO: OR 1.07, 95% CI: 0.27–4.26, $I^2=77\%$, $P=0.002$ (*Figure 2F*).

Table 1 Main characteristics of studies included in the meta-analysis

Study	Country	Study type	Sample size		Age (years)	Genotype and outcomes		Quality scores
			Case	Control		Case	Control	
Jin, 2001	China	Retrospective study	36	39	NA	AA: 24; AO: 11; OO: 1	AA: 24; AO: 15; OO: 0	7
Gomaa, 2018	Egypt	Retrospective study	160	80	Health group: 15.2±0.29	AA: 111; AO: 45; OO: 4	AA: 44; AO: 24; OO: 12	5
Schafrański, 2008	Brazil	Retrospective study	149	167	Health group: 38.90±13.56; RF group: 39.28±14.53	AA: 99; AO: 44; OO: 6	AA: 83; AO: 54; OO: 10	7
Col-Araz, 2013	Turkey	Retrospective study	38	40	Health group: 10.71±2.51; RF group: 10.37±3.81	AA: 21; AO: 13; OO: 4	AA: 26; AO: 14; OO: 0	7
Ramasawmy, 2008	Brazil	Retrospective study	90	281	RF group: 33.6±11.5	AA: 46; AO: 30; OO: 14	AA: 176; AO: 91; OO: 14	6

NA, not applicable; RF, rheumatic fever.

Discussion

Currently, some studies have reported the association between MBL2 and RF, but none of them reached a reliable conclusion. We investigated those inconsistent results, potentially pooling those inconsistent results. The present meta-analysis included 5 relevant studies involving 1,030 subjects to ensure a sufficient sample. Pooled results demonstrated that there is no association between MBL2 and RF. Most of our pooled results showed significant heterogeneity; unfortunately, it is not appropriate to carry out a subgroup analysis or meta-regression because only five studies were included. Finally, to minimize the probability of type I errors, a random-effects model was utilized for counting the effect size.

A previous study has found three common polymorphic areas in MBL2 (21): Allele B at codon 54 (G54D), allele C at codon 57 (G57E), and allele D at codon 52 (R52C). The mutated allele not only failed to activate the complement pathway, but also damaged the stability of *MBL2* gene (22-24). The mutant allele (include B, C, and D) of MBL2 is also named “allele O”. Besides, individuals who were heterozygous for MBL A allele and the dysfunctional allele B, allele C and allele D had a 5 to 20-fold reduction in MBL because of the gene product of MBL mutated allele is clearly dominant negative (12-14). Wild-type MBL2 A is the functional monomers that plays an important role in activating complements and macrophages, and MBL2 is closely related to infection and cardiovascular disease (25), so we guess that gene type may also play a crucial role in

protection from the diseases. Previous studies have also pointed that MBL-2 had a potential influence on immune system and clinical indication (12). MBL2 is associated with a wide range of micro-organisms, such as diverse *Candida* species, *Aspergillus fumigatus* and *Staphylococcus aureus* (26). For instance, as complementary host antifungal defense mechanisms may play an important role in vaginal mucosa (27), a normal MBL polymorphism would benefit the host, especially women in reproductive age (28).

However, in our study, we found that there is no association between RF and MBL2. One included study from Schafrański *et al.* (18) included patients with RF with or without RHD. In their study, they also found that there was no difference in gene expression between RF patients with or without RHD. Also, in the study of Messias *et al.* (29), they included patients with RF and RHD, but the results showed that there was no difference in the genotype of RF and allele, which was consistent with the study of Schafrański *et al.* (18). However, in Gomaa’s study (17), they found that B allele would be a protective factor against rheumatic carditis, and B allele could be applied in the differentiation between RF patients with or without RHD. Paradoxically, the serum levels of MBL2 were associated with the opsonization of complement-related immune complexes (30), so the low serum levels of MBL2 may lead to tissue damage and the deterioration of the prognosis. We speculate that patients with RF with B allele may have faster disease progression.

As a previous study reported that MBL2 could add the susceptibility and severity of some rheumatic diseases (31),

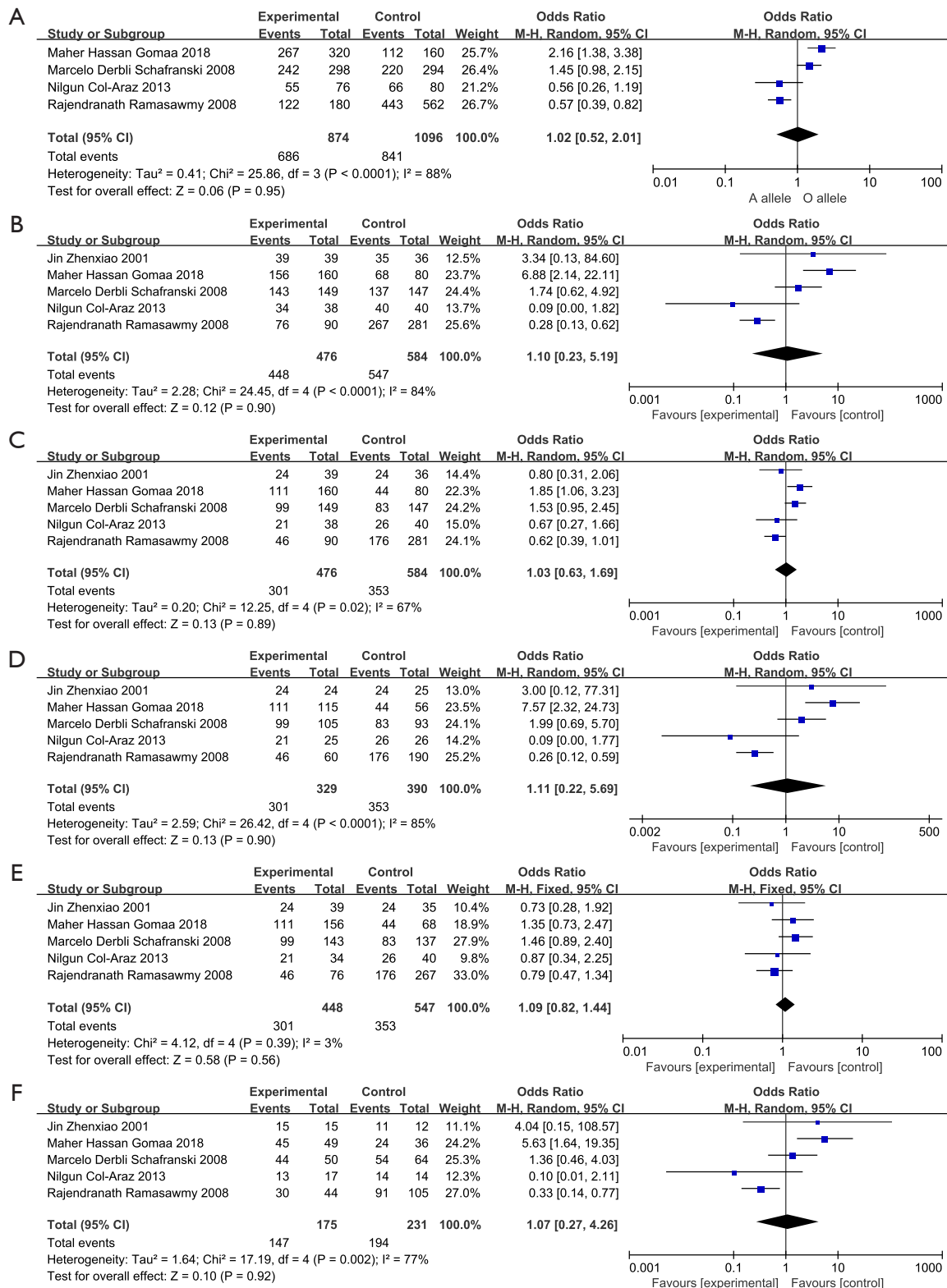


Figure 2 Forest plots of *MBL2* gene polymorphism in RF. (A) A vs. O; (B) AA + AO vs. OO; (C) AA vs. AO + OO; (D) AA vs. OO; (E) AA vs. AO; (F) AO vs. OO. RF, rheumatic fever.

low MBL2 serum level and deficient *MBL2* gene were associated with a higher incidence of acute cellular rejection (32). On the contrary, study found that *MBL2* gene has no impact on antibody mediated rejection, patient death, early graft dysfunction or loss. We guess that there is no significant association between *MBL2* gene and RF, but once rheumatic disease progresses to RHD and RA, *MBL2* gene can be associated with it.

Although some conclusions were made in this study, there are some limitations should be noticed by clinicians. First, the interaction between ethnicity and *MBL2* was not clear, and we included different ethnicity like Chinese, Brazilian, Egyptians and Turks, so further studies are needed to validate the relationship between ethnicity and *MBL2*. Second, we are unable to perform further subgroup analysis to find out the reason of heterogeneity, so we cannot discuss the potential factors (Race, age, region, gender, smoking, economic level and so on) that may have some impact on our pooled results. Third, previous studies have concluded that the function of a single gene may be influenced due to genetic polymorphisms. Four, the level of serum *MBL2* may also have some impact on the prognosis of patients with RF. Due to those limitations, our results are relatively weak.

Our study suggests that there is no association between *MBL2* gene and RF. However, serum *MBL2* may have an impact on patients with RF and other factors should be considered as well, so further high-quality evidence is needed to verify current conclusion.

In conclusion, we found that there is no association between RF and *MBL2*. However, although *MBL2* alleles do contribute to rheumatic etiology, we speculate that patients with RF with B allele may have faster disease progression. Because only five studies were included and the weak effect of the *MBL2* gene, further studies are needed to verify if *MBL2* genotypes could be a marker for RF and other rheumatic diseases.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <https://jxym.amegroups.com/article/view/10.21037/jxym-21-39/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jxym.amegroups.com/article/view/10.21037/jxym-21-39/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Erdem G, Mizumoto C, Esaki D, et al. Group A streptococcal isolates temporally associated with acute rheumatic fever in Hawaii: differences from the continental United States. *Clin Infect Dis* 2007;45:e20-4.
2. Carapetis JR, Currie BJ, Mathews JD. Cumulative incidence of rheumatic fever in an endemic region: a guide to the susceptibility of the population? *Epidemiol Infect* 2000;124:239-44.
3. Wyber R, Zühlke L, Carapetis J. The case for global investment in rheumatic heart-disease control. *Bull World Health Organ* 2014;92:768-70.
4. Ralph AP, Carapetis JR. Group a streptococcal diseases and their global burden. *Curr Top Microbiol Immunol* 2013;368:1-27.
5. Watkins DA, Johnson CO, Colquhoun SM, et al. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990-2015. *N Engl J Med* 2017;377:713-22.
6. Guilherme L, Ramasawmy R, Kalil J. Rheumatic fever and rheumatic heart disease: genetics and pathogenesis. *Scand J Immunol* 2007;66:199-207.
7. Yamamoto K, Okada Y, Suzuki A, et al. Genetics of rheumatoid arthritis in Asia--present and future. *Nat Rev Rheumatol* 2015;11:375-9.
8. Sastry K, Herman GA, Day L, et al. The human

- mannose-binding protein gene. Exon structure reveals its evolutionary relationship to a human pulmonary surfactant gene and localization to chromosome 10. *J Exp Med* 1989;170:1175-89.
9. Garred P, Larsen F, Seyfarth J, et al. Mannose-binding lectin and its genetic variants. *Genes Immun* 2006;7:85-94.
 10. Turner MW. The role of mannose-binding lectin in health and disease. *Mol Immunol* 2003;40:423-9.
 11. Bouwman LH, Roep BO, Roos A. Mannose-binding lectin: clinical implications for infection, transplantation, and autoimmunity. *Hum Immunol* 2006;67:247-56.
 12. Tong X, Wan Q, Li Z, et al. Association between the mannose-binding lectin (MBL)-2 gene variants and serum MBL with pulmonary tuberculosis: An update meta-analysis and systematic review. *Microb Pathog* 2019;132:374-80.
 13. Nedovic B, Posteraro B, Leoncini E, et al. Mannose-binding lectin codon 54 gene polymorphism and vulvovaginal candidiasis: a systematic review and meta-analysis. *Biomed Res Int* 2014;2014:738298.
 14. Ramasawmy R, Spina GS, Fae KC, et al. Association of mannose-binding lectin gene polymorphism but not of mannose-binding serine protease 2 with chronic severe aortic regurgitation of rheumatic etiology. *Clin Vaccine Immunol* 2008;15:932-6.
 15. Marzetti V, Di Battista C, Ferrante R, et al. MBL2 and FCN2 gene polymorphisms in a cohort of Italian children with rheumatic fever: A case-control study. *Semin Arthritis Rheum* 2017;47:264-8.
 16. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
 17. Gomaa MH, Ali SS, Fattouh AM, et al. MBL2 gene polymorphism rs1800450 and rheumatic fever with and without rheumatic heart disease: an Egyptian pilot study. *Pediatr Rheumatol Online J* 2018;16:24.
 18. Schafranski MD, Pereira Ferrari L, Scherner D, et al. High-producing MBL2 genotypes increase the risk of acute and chronic carditis in patients with history of rheumatic fever. *Mol Immunol* 2008;45:3827-31.
 19. Col-Araz N, Pehlivan S, Baspinar O, et al. Association of macrophage migration inhibitory factor and mannose-binding lectin-2 gene polymorphisms in acute rheumatic fever. *Cardiol Young* 2013;23:486-90.
 20. Jin Z, Ji Z, Hu J. Mannose-binding lectin gene site mutations and the susceptibility of rheumatic heart disease. *Zhonghua Yi Xue Za Zhi* 2001;81:1284-6.
 21. Ekşi, F, Pehlivan. S, Erdoğan MB, et al. MBL2 and MIF gene polymorphisms in cardiovascular patients with atherosclerotic lesions undergoing heart valve replacement. *Biotechnol Biotechnol Equip* 2017;31:1173-7.
 22. Hegele RA, Busch CP, Young TK, et al. Mannose-binding lectin gene variation and cardiovascular disease in Canadian Inuit. *Clin Chem* 1999;45:1283-5.
 23. Turner MW. Mannose-binding lectin (MBL) in health and disease. *Immunobiology* 1998;199:327-39.
 24. Ezekowitz RA. Genetic heterogeneity of mannose-binding proteins: the Jekyll and Hyde of innate immunity? *Am J Hum Genet* 1998;62:6-9.
 25. Queiroz MA, Gomes ST, Almeida NC, et al. Mannose-binding lectin 2 (Mbl2) gene polymorphisms are related to protein plasma levels, but not to heart disease and infection by Chlamydia. *Braz J Med Biol Res* 2016;49:e5519.
 26. Neth O, Jack DL, Dodds AW, et al. Mannose-binding lectin binds to a range of clinically relevant microorganisms and promotes complement deposition. *Infect Immun* 2000;68:688-93.
 27. De Luca A, Carvalho A, Cunha C, et al. IL-22 and IDO1 affect immunity and tolerance to murine and human vaginal candidiasis. *PLoS Pathog* 2013;9:e1003486.
 28. Romani L. Immunity to fungal infections. *Nat Rev Immunol* 2011;11:275-88.
 29. Messias Reason IJ, Schafranski MD, Jensenius JC, et al. The association between mannose-binding lectin gene polymorphism and rheumatic heart disease. *Hum Immunol* 2006;67:991-8.
 30. Figueiredo GG, Cezar RD, Freire NM, et al. Mannose-binding lectin gene (MBL2) polymorphisms related to the mannose-binding lectin low levels are associated to dengue disease severity. *Hum Immunol* 2016;77:571-5.
 31. Jacobsen S, Garred P, Madsen HO, et al. Mannose-binding lectin gene polymorphisms are associated with disease activity and physical disability in untreated, anti-cyclic citrullinated peptide-positive patients with early rheumatoid arthritis. *J Rheumatol* 2009;36:731-5.
 32. Giang NT, van Tong H, Quyet D, et al. Complement protein levels and MBL2 polymorphisms are associated with dengue and disease severity. *Sci Rep* 2020;10:14923.

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