DOI: https://doi.org/10.30841/2786-720X.3.2025.339910
UDC 616.127-089:616.12-002

The role of genetic factors in pathogenesis of acute rheumatic fever and rheumatic heart disease (Review of the literature)

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Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) still belong to diseases whose pathogenesis remains unclear. The issue of its multifactorial nature is widely discussed in the literature. Genetic, environmental, immunological, hormonal, infectious and other factors actively participate in the development of the rheumatic process. Unlike classical genetic diseases, in which many different genes and their combinations predispose to the development of the disease, ARF is a genetically heterogeneous disease, which is primarily caused by genetic imperfection of immunoregulatory processes. According to numerous studies, the risk of rheumatic process development is associated with the carriage of the major histocompatibility complex antigen class II human leukocyte antigen (HLA)-DR4 and HLA-DR1, which includes more than 20 alleles. The roles of other genetic factors not directly associated with HLA-DR are also actively discussed. These include gene polymorphism of mannose binding lectin-2 (*MBL2*), ficolin-1 (*FCN1*), and ficolin-2 (*FCN2*), tumor necrosis factor (*TNF*), interleukin-1 receptor antagonist (*IL1RN*), transforming growth factor β1 (*TGFβ1*), etc. However, it should be noted that the results available to date are contradictory, some of them have a number of limitations related to the sample size.
Thus, according to the literature data, we analyzed the direct connection of these genes with predisposition to ARF and RHD. It can be concluded that further study of the presence of such genes in patients with rheumatic process is very relevant at the moment in order to assess their impact on the possibility of disease development, variants of the clinical course, treatment and prognosis of this pathology.
Keywords: *acute rheumatic fever, rheumatic heart disease, gene polymorphism, major histocompatibility complex.*

Роль генетичних факторів у патогенезі гострої ревматичної лихоманки та ревматичної хвороби серця (Огляд літератури)

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Гостра ревматична лихоманка (ГРЛ) та ревматична хвороба серця (РХС) досі належать до захворювань, патогенез яких залишається неповністю зрозумілим, питання їхньої багатофакторної природи широко обговорюється в літературі. Генетичні, екологічні, імунологічні, гормональні, інфекційні та інші фактори активно беруть участь у розвитку ревматичного процесу. На відміну від класичних генетичних захворювань, при яких багато різних генів і їхніх комбінацій сприяють виникненню та прогресуванню патології, ГРЛ є генетично гетерогенним захворюванням, яке переважно обумовлено генетичною недосконалістю імунорегуляторних процесів. Згідно з численними дослідженнями, ризик розвитку ревматичного процесу пов'язаний із носієм антигену головного комплексу гістосумісності класу II human leukocyte antigen (HLA)-DR4 та HLA-DR1, який включає понад 20 алелів. Активно обговорюється також роль інших генетичних факторів, не пов'язаних безпосередньо з HLA-DR. До них належать поліморфізм генів манозозв'язувального лектину-2 (*MBL2*), фіколіну-1 (*FCN1*) та фіколіну-2 (*FCN2*), фактора некрозу пухлини (*TNF*), антагоніста рецептора інтерлейкіну-1 (*IL1RN*), трансформівного фактора росту β1 (*TGFβ1*) тощо. Однак слід зазначити, що наявні на сьогодні результати досліджень є суперечливі, деякі з них мають низку обмежень, що пов'язано з розміром вибірки.
Отже, згідно з даними літератури, проаналізовано прямий зв'язок цих генів зі схильністю до ГРЛ та РХС. Можна зробити висновок, що на сьогодні подальше вивчення наявності таких генів у пацієнтів із ревматичним процесом є дуже актуальним для оцінювання їхнього впливу на ризик розвитку патології, клінічні варіанти перебігу, ефективність терапії та прогноз для хворих.
Ключові слова: *гостра ревматична лихоманка, ревматична хвороба серця, поліморфізм генів, головний комплекс гістосумісності.*

Acute rheumatic fever (ARF) is an immune-mediated complication of tonsillopharyngitis caused by group A streptococci (GAS) [1].

Despite widespread preventive measures, the statistics remain quite unfavorable. About 470,000 new cases of ARF are registered annually, with a higher proportion of the disease occurring in developing countries with higher rates of untreated or inadequately treated GAS infections [2, 3].

Over the past decades, the prevalence of ARF and rheumatic heart disease (RHD) had decreased significantly in developed countries. Currently, the burden of RHD predominantly related to developing countries, but also in high-income countries among the elderly and immigrants, which seems especially important in the modern reality [4, 5].

A major long-term consequence of ARF is RHD, which carries significant morbidity and mortality [1, 2].

RHD control programs were successfully implemented in some low- and middle-income countries in the second half of the 20th century, which prompted the World Health Organization (WHO) and other organizations to reduce the scope of their ARF / RHD activities by the early 2000s. A number of countries have seen prominent

reductions in mortality, which can be explained by the implementation of surveillance programs and improvements in local and international health systems [2, 6–8].

However, the statistical data of developing countries support the thesis that RHD remains an important, but potentially preventable cause of cardiovascular mortality and disability in these countries. Worldwide, more than 275,000 deaths are associated with RHD each year [9, 10].

Despite the improvements, related to special programs, many regions, including Africa, South Asia and the Pacific Islands, continue to report high rates of RHD prevalence and mortality [5, 6, 11, 12].

The researchers noted that there is growing interest in the burden of RHD, driven in part by the availability of screenings, including echocardiography-based screening in countries and regions where the disease is endemic and the growing need to achieve cardiovascular health targets [13, 14].

In 2013, WHO and the World Heart Federation called for a 25% reduction in mortality in people under 25 years due to cardiovascular causes, including RHD, by 2025. In previous years the annual mortality rate from chronic RHD was 1.5%, reaching a maximum in the countries of the Asian region (3.3%) [1, 15].

Since the problem still remains relevant, the study of the factors underlying the pathogenesis of the disease is certainly capable of having an effective impact on the prevention of serious consequences of GAS infection and ARF [2, 16, 17].

The pathogenesis of ARF and RHD is multifaceted, so, it requires detailed study, but the data obtained to date indicate that the inflammatory process is an integral part of it [9, 18].

The basic mechanisms of the rheumatic process include the development of a complex cascade of changes. The main part of them are the inflammatory and proliferative processes of varying intensity and significance, which unfold meanwhile disease progresses. The essence of tissue disorders in ARF is the systemic disorganization of connective tissue in combination with specific proliferative and non-specific exudative-proliferative reactions, as well as damage to the vessels of the microcirculatory system. Thus, the main zone that becomes the site for extensive pathological manifestations should be considered connective tissue, primarily the heart [1, 17, 19].

J. Osowicki et al. (2021) noted, that since the pathophysiological processes in ARF are based on an abnormal immune response of the body to GAS infection, characterized by the so-called "molecular mimicry", i.e. antigenic similarity of GAS and the body's own tissues, genetic factors are of great importance. According to L. S. A. Passos et al. (2021), as a result of molecular mimicry, the phenomenon of cross-reacting antibodies occurs – antibodies produced against the infection or T cells against the infectious pathogen attack the host's own cells, recognizing them as a target. In the case of ARF, heart and brain tissues are considered the main carriers of target antigens for cross-reacting antibodies. Thus, in ARF, the defense mechanism turns against the host [18, 20].

But not in all persons with streptococcal infection ARF develops. According to the classic theory some predisposing factor are needed to stimulate the immune-mediated inflammation by A streptococcal infection. Approximately 60% of ARF patients develop RHD, thus a chronic aseptic inflammatory process in a genetically predisposed host plays an important role in the progression of disease [12, 20, 21].

P. D. Bright et al. (2016) claimed that the molecular mechanisms underpinning the progression of ARF to RHD are poorly understood. They noted that cross-reactivity initiated by molecular mimicry may not be the mechanism of progression, since autoantibodies have been detected in healthy individuals and cardiac myosin is not expressed at the cell surface [22]. A. Efstratiou et al. (2016) and D. Sika-Paotonu et al. (2016) in their works emphasized that there is a proven association between GAS infection and RHD, the triggered autoimmune process in RHD can occur autonomously after removing the stimulus [9, 17].

S. Zhuang et al. (2025) came to a conclusion, that available data from studies of families with individuals susceptible to developing ARF have shown that this susceptibility is characterized by hereditary tendencies and loci with limited penetrance. The authors noted that, interestingly, this inheritance does not follow a classical Mendelian pattern, although concordance of phenotype among dizygotic twins supports a hereditary component to ARF [23].

In addition, the class I human leukocyte antigen (HLA) allele HLA-B5 is associated with formation of immune complexes, which are the crucial part of ARF pathogenesis. These associations indicate that genetic alterations of the Fc receptor (*FcR*) genes (*low-affinity immunoglobulin-γ Fc region receptor IIa*, *FCGR2A*). This mechanism is one of the potential causes for failure of clearance of immune complexes. In number of studies, it was noted that noneffective elimination of immune complexes might play an important part in ARF and RHD pathogenesis RHD, which is estimated to affect 33.4 million people and results in 10.5 million disability-adjusted life-years lost globally [24–26].

B. Muhamed et al. (2020) and D. Kumar et al. (2023) claimed that the components of the class II HLA system are responsible for triggering adaptive immune responses via the T cell receptor by being expressed on the surface of antigen-presenting cells. The DR7 allele is most commonly associated with these conditions and is universally associated with ARF and RHD [26, 27].

D. Kumar et al. (2023) found out a significant difference was found between the cases and controls for HLA-DRB1*15:01 ($p = 0.002$), HLA-DRB4*01:01 ($p = 0.045$), HLA-DRB5*01:01 ($p = 0.017$), and HLA-DQB1*02:01 ($p = 0.005$). Their study suggests that HLA class II haplotypes may be a useful marker for predicting clinical outcome in patients with rheumatic fever, as they provide information about the molecular mechanism of RHD. The authors emphasized that this knowledge could serve as a basis for new treatments or vaccine development. However, they noted that larger studies in different populations should be conducted to address this issue [27].

The results of a meta-analysis conducted by M. Poomarimuthu et al. (2022), showed that the presentation of autoimmune peptides by HLA-DRB1*07:01 alleles, which are associated with susceptibility, and HLA-DRB1*15:01 alleles, which play a protective role, is of critical importance in the pathogenesis of rheumatic fever [28].

The genome-wide association study involved the indigenous population of Australia using the 550K Illumina Infinium Human Core Exome platform was conducted. L. A. Gray et al. (2017) by observation of 398 cases related to RHD, found out identified HLA-DQA1 (rs9272622)

as the most linked association. In this study in a list of risk allele HLA-DQB1*06:01 was placed, and as protective allele the researchers noted HLA-DQA1*03:01. It was also revealed that there are 2 risk and 1 protective haplotypes: HLA-DQA1*01:01–DQB1*05:03 and HLA-DQA1*01:03–DQB1*06:01 are the risk haplotypes and HLA-DQA1*03:01–DQB1*04:02 is the protective one. According to authors data, these haplotypes played important role in the development of disease. The study also identified HLA-DRB1*08:03 (odds ratio = 1.06; p = 0.005) as a susceptibility locus [24].

In some small studies for candidate markers, the reports about relationship between RHD and HLA were presented.

D. Kumar et al. (2023) describing the situation in various populations, concluded that associations have some differences: in a study conducted in Japan, patients with RHD demonstrated an association with HLA-DQA1*01:04 and DQB1*05:03, in studies covering Turkish and Pakistani populations, HLA-DRB1*07:01 was identified as a risk allele. The same allele was also identified in the Latvian population, but HLA-DRB1*08:01 has not been reported before. The authors also emphasized that an association of the HLA-DRB1*07:01–DQA1*02:01 haplotype with rheumatic mitral valve defects was established in the Egyptian population. HLA-DRB1*01:01, HLA-DRB1*13:01, HLA-DRB1*15:01, and HLA-DQB1*08:01 were also included in the risk allele groups [27].

J. Oliver et al. (2021) reported about protective HLA alleles in various populations. As an example, HLA-DRB1*04:01–DQA1*03:01 might be noted for Turkish patients as well as HLA-DRB1*06:01–DQB1*06:01 for individuals from Latvia [21]. L. A. Gray et al. (2017) revealed that HLA-DQA1*03:01 and HLA-DQA1*03:01–DQB1*04:02 haplotypes demonstrated the protective role among Australian indigenous population [24].

J. A. Osgood et al. (2018) noted that in recent years, genome-wide association studies (GWAS) have played a key role in identifying genetic loci responsible for susceptibility to various severe diseases with complex pathogenesis and poor prognosis [30]. L. A. Gray et al. emphasized that in the course of such studies, interesting relationships have been established between susceptibility loci in RHD, which are predominantly localized in critical immunological pathways and are common with other autoimmune diseases. The authors believed that natural positive selection has developed in the course of evolution based on the role of these loci in the fight against infectious diseases [24].

T. Parks et al. (2017) descibed three GWASs conducted among patients with RHD which revealed a number of interrelations between HLA and immunoglobulin heavy (IGH) loci. The first GWAS related to RHD was carried out by Pacific Islands Rheumatic Heart Disease Genetics Network in 2017. In the framework of the study, 1,006 indigenous people in various countries of Oceania were examined using the Illumina HumanCore-300K Platform. This tool is considered a low-density GWAS chip. Based on their data, the authors highlighted that using low-density GWAS could be useful, suggesting that fewer variants would be needed due to linkage failures in populations from Oceania countries where larger distances matter compared to populations from other regions. In addition, the new susceptibility allele was detected in the IGH locus (IGHV4-61*02 allele), which is characterized with an association with a 1.4-fold increased RHD risk [31].

M. Gutierrez-Arcelus et al. (2016) noted that the IGH locus is a challenging region to study because data of its polymorphisms is limited. Given that only 16 genotype variants were in fact used in their study (actually, the locus has 1,255 kilobases), and that it is poorly labeled in current arrays, research in this area faces significant hurdles. However, it is undeniable that discovering the genome-wide significance of a specific gene segment may have invaluable potential for understanding the subtle immunogenetic mechanisms of RHD development [33].

Polymorphisms in several genes coding for immune-related proteins have been associated with ARF and RHD susceptibility.

One of important pathways implicated in RHD is the lectin pathway, which includes mannose binding lectin-2 (*MBL2*), ficolin-1 (*FCN1*), and ficolin-2 (*FCN2*) [34].

Some researchers evaluated minor *FCN1* promoter variants. S. J. Catarino et al. (2018) noted, that variants of *FCN1* have a protective role in cases of rheumatic fever due to the fact that they encourage elimination of bacteria. The other mechanisms include the increasing protein levels as well as gene expression. In their work, the authors emphasized, that two polymorphisms (–1981A and –144A) are associated with increased risk of RHD (the interrelations between these alleles and lesions such as valvular stenosis and mitral insufficiency were found out). The researchers noted that on the other hand, four alleles (–1981A, 542A, –144A, and –33T) are characterized by increasing of gene expression, so, they may be considered as protective. They suggested, that FCN1 has dual role in the development of RHD due to fact that these alleles probably contribute to chronic inflammation and tissue injury, thus may also predispose the patients to heart lesions [35]. Thus, it highlights the complexity of the gene-environment interaction in RHD after GAS infection.

There is evidence that FCN2 has the ability to bind to lipoteichoic acid. This acid is one of the components of the cell wall of Streptococcus pyogenes, as well as all gram-positive bacteria. Since there is no doubt that GAS is the etiologic agent of rheumatism, this pathogenetic mechanism should also be considered in the context of complications, the most severe of which is chronic RHD. When studying polymorphisms in the promoter region of the *FCN2* gene (at positions –986/–602 and –4), it was established that there is an association of the haplotype –986/–602/–4 G/G/A with RHD, since this polymorphism was observed more often in patients of this group [36].

The role of other protein – mannose-binding protein C2 (*MBL2*) is debatable. V. Marzetti et al. (2017), studying 50 Caucasian patients with ARF assessed the role of mannose-binding protein C2 gene (exon 1, codons 52, 54, and 57) and FCN2 gene (promoter region at position –986, –602, and –4). They also found out that a –986 GG and –4 GG genotypes have protective impact in cases with rheumatic fever. At the same time, it has been established that –4 AG genotype has close interrelations with rheumatic carditis. However, in their data the possibility of *MBL2* polymorphisms' role in pathogenetic mechanisms and clinical manifestations of rheumatic fever had not been confirmed [37].

In the study of M. Poomarimuthu et al. (2018), the participation of IL-17, also called IL-17A, which is released by a subset of T helper cells known as Th17 cells, in pathogenesis of rheumatic process were evaluated. The *IL17A* promoter polymorphism (rs2275913) demonstrated association with lesions of mitral valve [38]. The angiotensin I-converting enzyme gene insertion/deletion polymorphism is a locus which demonstrates a number of different associations in various population groups. The meta-analysis of Y. Tian et al. (2016), covered 9 studies did not show any correlation RHD (this meta-analysis which was conducted recently included 1,333 cases of RHD as well as 1,212 individuals for control from 7 different populations) [39]. In some studies, the role of cytotoxic T-lymphocyte protein 4, tumor necrosis factor, toll-like receptor 2, transforming growth factor β1, interleukin-1 receptor antagonist, in development of ARF and RHD were proven [40, 41].

Further understanding of genetic susceptibility to ARF is likely to come from large multi-ethnic genome studies rather than studies from a single region. As can be seen, the results are quite heterogeneous, which complicates the implementation of the obtained and identified genetic discoveries in clinical practice. In addition, L. A. Gray et al. (2017) noted, that some established associations are often not confirmed in subsequent studies: for example, the relationship between IGHV4-61*02 and the rheumatic process identified in the populations of Oceania was not confirmed in the indigenous Australian population. The authors emphasized that, interestingly, both populations are considered indigenous, so it is possible that genetic heterogeneity may have influenced the results to some extent [24].

J. A. Osgood et al. (2018) claimed that it should not be overlooked that the effects of various GAS strains also differ, as do the protective responses and response interactions of the risk-associated HLA alleles [30]. C. Terao et al. (2018) provided the hypothesis about the possibility of epistasis between HLA alleles and non-HLA variants, which may provide a rationale for explaining the discrepancies [42]. According to T. Parks et al. (2017), overall, the HLA and IGH associations do not refute the theory of molecular mimicry, which is currently the underlying mechanism of RHD pathogenesis [31].

As noted in work of B. Muhamed et al. (2020), recently, the candidate gene approach has been discussed in the context of hypotheses aimed at predicting a potential gene or locus that may be of interest in the study of pathogenetic mechanisms. However, according their conclusion, given that in cases of pathologies where some aspects of pathogenesis are still unclear, this method does not always identify in detail the complete genetic basis of the disease [26].

M. Gutierrez-Arcelus et al. (2016) indicated that candidate gene case-control approaches undoubtedly play an important role, since they have so far allowed to identify related genetic loci associated with various autoimmune diseases. It is undeniable that the above techniques have shed light on the molecular mechanisms of many diseases. The authors claimed that, unfortunately, according to the available literature, compared to autoimmune pathologies, relatively few candidate-gene studies were performed for ARF and RHD. They emphasized that most associations are not confirmed in independent populations, making them not fully verified [33].

One of the immunomodulatory genes is interleukin-10. A. M. Abdallah et al. (2016) revealed that three promoter polymorphisms in interleukin-10 (–1082A>G, –829C>T and –592C>A) were identified in patients with RHD from different populations. These studies suggested that the IL10-ACC promoter haplotype plays a protective role. At the same time, the authors noted that this haplotype is associated with increased IL-10 production, which may serve as a basis for conclusions about the role of this locus [40].

W. Dai et al. (2018) reported that this protective role has been somewhat questioned, as a meta-analysis of three different populations showed statistically insignificant results ($p = 0.08$) [41].

A. M. Abdallah et al. (2016), in one of their study examined the macrophage migration inhibitory factor (MIF) promoter polymorphisms –173C and –794 (5–8 CATT repeats) in a Saudi Arabian population. The authors found that these polymorphisms were correlated with the age of RHD onset. There is association between higher MIF expression in T cell lines and C allele at –173 [43]. As in some of the studies mentioned above, the authors encountered a dual effect of these promoter polymorphisms on RHD. Late onset of the disease and lower risk were found for the –173C allele, while the –794 CATT5 allele was also associated with a low risk. However, the researchers noted that the –794 CATT6 allele was associated with an increased risk of RHD. These data were true for the studied population, which requires the involvement of other regions to confirm the universality of the hypothesis [43].

In the other study, M. Gutierrez-Arcelus et al. (2016) indicated the dual effect of these alleles established for other autoimmune diseases [33].

P. D. Bright et al. (2016) reported about a consistently high production of IL-1β was found against the background of GAS infection by mononuclear cells. These cells were obtained from the peripheral blood of a patient with ARF, in whom this production was significantly reduced after treatment with hydroxychloroquine. These new findings open up broader perspectives in the study of the pathogenetic mechanisms of RHD, the role of inflammasomes in the development of RHD, as well as new opportunities in the development of therapeutic approaches aimed at this pathway [22]. However, it should be noted that the results available to date are contradictory, some of them have a number of limitations related to the sample size.

Thus, according to the literature data, we analyzed the direct connection of these genes with predisposition to ARF and RHD. It can be concluded that further study of the presence of such genes in patients with rheumatic process is very relevant at the moment in order to assess their impact on the possibility of developing disease, variants of the clinical course, treatment and prognosis of this pathology.

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REFERENCES

1. Chowdhury MDS, Koziatek CA, Tristram D. Acute Rheumatic Fever [Internet]. In: StatPearls Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK594238/.
2. World Health Organization. WHO guideline on the prevention and diagnosis of rheumatic fever and rheumatic heart disease [Internet]. Geneva: WHO; 2024. 53 p. Available from: https://www.who.int/publications/i/item/9789240100077.
3. Woldu B, Bloomfield GS. Rheumatic heart disease in the twenty-first century. Curr Cardiol Rep. 2016;18(10):96. doi: 10.1007/s11886-016-0773-2.
4. Coffey PM, Ralph AP, Krause VL. The role of social determinants of health in the risk and prevention of group A streptococcal infection, acute rheumatic fever and rheumatic heart disease: A systematic review. PLoS Negl Trop Dis. 2018;12(6):e0006577. doi: 10.1371/journal.pntd.0006577.
5. De Dassel JL, Ralph AP, Carapetis JR. Controlling acute rheumatic fever and rheumatic heart disease in developing countries: Are we getting closer? Curr Opin Pediatr. 2015;27(1):116-23. doi: 10.1097/MOP.0000000000000164.
6. Coffey S, Roberts-Thomson R, Brown A, Carapetis J, Chen M, Enriquez-Sarano M, et al. Global epidemiology of valvular heart disease. Nat Rev Cardiol. 2021;18(12):853-64. doi: 10.1038/s41569-021-00570-z.
7. Oliver JR, Pierse N, Stefanogiannis N, Jackson C, Baker MG. Acute rheumatic fever and exposure to poor housing conditions in New Zealand: A descriptive study. J Paediatr Child Health. 2017;53:358-64. doi: 10.1111/jpc.13421.
8. Ralph AP, Kelly A, Lee AM, Mungatopi VL, Babui SR, Budhathoki NK, et al. Evaluation of a community-led program for primordial and primary prevention of rheumatic fever in remote Northern Australia. Int J Environ Res Public Health. 2022;19(16):10215. doi: 10.3390/ijerph191610215.
9. Efstratiou A, Lamagni T. Epidemiology of Streptococcus pyogenes [Internet]. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. Streptococcus pyogenes: Basic Biology to Clinical Manifestations, Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK343616/.
10. Ochodo EA, Olwanda EE, Blose N, Hohlfeld A, Engel M, Kredo T, et al. Accuracy of signs and symptoms to identify streptococcal skin infection in participants with suspected bacterial skin infection [Internet]. Geneva: WHO; 2023. 427 p. Available from: https://iris.who.int/handle/10665/379278.
11. Thomas N, Kaur S, Saxena A. Evaluation of a nurse-led intervention to improve adherence to secondary prevention of rheumatic heart disease. Br J Cardiac Nursing. 2022;17(2):1-9. doi: 10.12968/bjca.2021.0115.
12. Adem A, Dukessa GT, Jarso H, Reta W. Rheumatic heart disease patients' adherence to secondary prophylaxis and associated factors at hospitals in Jimma Zone, Southwest Ethiopia: A Multicenter Study. Patient Prefer Adherence. 2020;14:2399-406. doi: 10.2147/ppa.S281413.
13. Telford LH, Abdullahi LH, Ochodo EA, Zuhlke LJ, Engel ME. Standard echocardiography versus handheld echocardiography for the detection of subclinical rheumatic heart disease: a systematic review and meta-analysis of diagnostic accuracy. BMJ Open. 2020;10:e038449. doi: 10.1136/bmjopen-2020-038449.
14. World Health Organization. Screening programs: A short guide [Internet]. Geneva: WHO; 2020. 70 p. Available from: https://iris.who.int/bitstream/handle/10665/330829/9789289054782-eng.pdf.
15. World Health Organization. Global Health Estimates 2021: Deaths by cause, age, sex, by country and by region, 2000–2021. Geneva, WHO; 2024. Available from: https://www.who.int/data/global-health-estimates.
16. Baker MG, Gurney J, Moreland NJ, Bennett J, Oliver J, Williamson DA, et al. Risk factors for acute rheumatic fever: A case-control study. Lancet Reg Health West Pac. 2022;26:100508. doi: 10.1016/j.lanwpc.2022.100508.
17. Sika-Paotonu D, Beaton A, Raghu A, Steer A, Carapetis J. Acute Rheumatic Fever and Rheumatic Heart Disease [Internet]. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. Streptococcus pyogenes: Basic Biology to Clinical Manifestations, Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK425394/.
18. Passos LSA, Nunes MCP, Aikawa E. Rheumatic heart valve disease pathophysiology and underlying mechanisms. Front Cardiovasc Med. 2021;7:612716. doi: 10.3389/fcvm.2020.612716.
19. Diamantino Soares AC, Araújo Passos LS, Sable C, Beaton A, Ribeiro VT, Gollob KJ, et al. Circulating cytokines predict severity of rheumatic heart disease. Int J Cardiol. 2019;289:107-09. doi: 10.1016/j.ijcard.2019.04.063.
20. Osowicki J, Azzopardi KI, Fabri L, Frost HR, Rivera-Hernandez T, Neeland MR, et al. A controlled human infection model of Streptococcus pyogenes pharyngitis (CHIVAS-M75): an observational, dose-finding study. Lancet Microbe. 2021;2(7):e291-9. doi: 10.1016/S2666-5247(20)30240-8.
21. Oliver J, Bennett J, Thomas S, Zhang J, Pierse N, Moreland NJ, et al. Preceding group A streptococcus skin and throat infections are individually associated with acute rheumatic fever: evidence from New Zealand. BMJ Glob Health. 2021;6(12):e007038. doi: 10.1136/bmjgh-2021-007038.
22. Bright PD, Mayosi BM, Martin WJ. An immunological perspective on rheumatic heart disease pathogenesis: more questions than answers. Heart. 2016;102:1527-32. doi: 10.1136/heartjnl-2015-309188.
23. Zhuang S, Guo D, Yu D. A mini review of the pathogenesis of acute rheumatic fever and rheumatic heart disease. Front Cell Infect Microbiol. 2025;15:1447149. doi: 10.3389/fcimb.2025.1447149.
24. Gray LA, D'Antoine HA, Tong SYC, McKinnon M, Bessarab D, Brown N, et al. Genome-wide analysis of genetic risk factors for rheumatic heart disease in aboriginal Australians provides support for pathogenic molecular mimicry. J Infect Dis. 2017;216(11):1460-70. doi: 10.1093/infdis/jix497.
25. Martin WJ, Steer AC, Smeesters PR, Keeble J, Inouye M, Carapetis J, et al. Post-infectious group A streptococcal autoimmune syndromes and the heart. Autoimmun Rev. 2015;14(8):710-25. doi: 10.1016/j.autrev.2015.04.005.
26. Muhamed B, Parks T, Sliwa K. Genetics of rheumatic fever and rheumatic heart disease. Nat Rev Cardiol. 2020;17(3):145-54. doi: 10.1038/s41569-019-0258-2.
27. Kumar D, Deepak R, Bhatt DD, Kumari L, Arumugam P, Kaur K, et al. Association of HLA class II DR/DQ alleles in children and adolescents with rheumatic heart disease from a tertiary care centre in North India. Indian Heart J. 2023;75(4):263-7. doi: 10.1016/j.ihj.2023.06.008.
28. Poomarimuthu M, Ramasamy T, Govindan R, Andiappan R, Nagarajan G, Kadiam S, et al. Association of HLA-DRB1 Alleles with Rheumatic Fever and Rheumatic Heart Disease: A Meta-analysis. Immunol Invest. 2022;51(2):221-32. doi: 10.1080/08820139.2020.1822864.
29. Auckland K, Mittal B, Cairns BJ, Garg N, Kumar S, Mentzer AJ, et al. The Human Leukocyte Antigen Locus and Rheumatic Heart Disease Susceptibility in South Asians and Europeans. Sci Rep. 2020;10(1):9004. doi: 10.1038/s41598-020-65855-8.
30. Osgood JA, Knight JC. Translating GWAS in rheumatic disease: Approaches to establishing mechanism and function for genetic associations with ankylosing spondylitis. Brief Funct Genomics. 2018;17(5):308-18. doi: 10.1093/bfgp/ely015.
31. Parks T, Mirabel MM, Kado J, Auckland K, Nowak J, Rautanen A, et al. Association between a common immunoglobulin heavy chain allele and rheumatic heart disease risk in Oceania. Nat Commun. 2017;8:14946. doi: 10.1038/ncomms14946.
32. Beltrame MH, Catarino SJ, Goeldner I, Boldt AB, de Messias-Reason IJ. The lectin pathway of complement and rheumatic heart disease. Front Pediatr. 2015;2:148. doi: 10.3389/fped.2014.00148.
33. Gutierrez-Arcelus M, Rich SS, Raychaudhuri S. Autoimmune diseases – connecting risk alleles with molecular traits of the immune system. Nat Rev Genet. 2016;17(3):160-74. doi: 10.1038/nrg.2015.33.
34. Kareem S, Jacob A, Mathew J, Quigg RJ, Alexander JJ. Complement: Functions, location and implications. Immunology. 2023;170(2):180-92. doi: 10.1111/imm.13663.
35. Catarino SJ, Andrade FA, Boldt ABW, Guilherme L, Messias-Reason IJ. Sickening or Healing the Heart? The Association of Ficolin-1 and Rheumatic Fever. Front Immunol. 2018;9:3009. doi: 10.3389/fimmu.2018.03009.
36. Elshamaa MF, Hamza H, El Rahman NA, Emam S, Elghoroury EA, Farid TM, et al. Association of ficolin-2 (FCN2) functional polymorphisms and protein levels with rheumatic fever and rheumatic heart disease: relationship with cardiac function. Arch Med Sci Atheroscler Dis. 2018;3:e142-e155. doi: 10.5114/amsad.2018.80999.
37. Marzetti V, Di Battista C, Ferrante R, Carlucci L, Balsamo M, Stuppia L, 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(2):264-8. doi: 10.1016/j.semarthrit.2017.04.006.
38. Poomarimuthu M, Elango S, Solomon PR, Soundrapandian S, Mariakuttikan J. Association of IL17 and IL23R gene polymorphisms with rheumatic heart disease in South Indian population. Immunol Invest. 2018;47(7):754-64. doi: 10.1080/08820139.2018.1493053.
39. Tian Y, Ge Z, Xing Y, Sun Y, Ying J. Correlation of angiotensin I-converting enzyme gene insertion/deletion polymorphism with rheumatic heart disease: a meta-analysis. Biosci Rep. 2016;36(6):e00412. doi: 10.1042/BSR20160151.
40. Abdallah AM, Alnuzha A, Al-Mazroea AH, Eldardear AE, AlSamman AY, Almohammadi Y, et al. IL10 Promoter Polymorphisms are Associated with Rheumatic Heart Disease in Saudi Arabian Patients. Pediatr Cardiol. 2016;37(1):99-105. doi: 10.1007/s00246-015-1245-y.
41. Dai W, Ye Z, Lu H, Su Q, Li H, Li L. Meta-analysis of the relationship between single nucleotide polymorphism of IL-10-1082G/A and rheumatic heart disease. Oncotarget. 2018;9(15):12343-50. doi: 10.18632/oncotarget.23901.
42. Terao C, Yoshifuji H, Matsumura T, Naruse TK, Ishii T, Nakaoka Y, et al. Genetic determinants and an epistasis of LILRA3 and HLA-B*52 in Takayasu arteritis. Proc Natl Acad Sci U S A. 2018;115(51):13045-50. doi: 10.1073/pnas.1808850115.
43. Abdallah AM, Al-Mazroea AH, Al-Harbi WN, Al-Harbi NA, Eldardear AE, Almohammadi Y, et al. Impact of MIF gene promoter variations on risk of rheumatic heart disease and its age of onset in Saudi Arabian patients. Front Immunol. 2016;7:98. doi: 10.3389/fimmu.2016.00098.

Стаття надійшла до редакції 21.04.2025. – Дата першого рішення 24.04.2025. – Стаття подана до друку 05.06.2025