Cardiol Cardiovasc Med 2021;5 (4): 446-453 *DOI: 10.26502/fccm.92920214*

Review Article

Unfurling the Role of Genetic Polymorphism in Rheumatic Heart Disease Pathogenesis

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Received: 09 August 2021; **Accepted:** 17 August 2021; **Published:** 31 August 2021

Citation: Shruti Sharma, Anuradha Chakraborti. Unfurling the Role of Genetic Polymorphism in Rheumatic Heart Disease Pathogenesis. Cardiology and Cardiovascular Medicine 5 (2021): 446-453.

Abstract

Rheumatic heart disease (RHD), an autoimmune disease sequel of rheumatic fever, which leads to dysfunction of the heart, is a major public health problem in developing countries that contributes to significant cardiac morbidity and mortality. High mortality was observed in low-income and middle-income countries and even in some groups living in high-income countries. Hence, elucidation of the pathogenic mechanisms in RHD, for therapeutic applications is of major concern and need of the hour. Although, molecular mimicry (MM) is the most established theory for RHD development, however contribution of other factors cannot be ignored. Studies have indicated the role of host-pathogen interacting proteins and immunological factors (T cells-cytokines and chemokines) in RHD, however not much information is available regarding role of polymorphic genes during RHD. The present review, specifically highlights the association of genetic polymorphism with disease manifestation.

Keywords: RHD; Pathogenesis; Molecular Mimicry; Genetic polymorphism

1. Introduction

Rheumatic heart disease (RHD) is the result of an autoimmune sequelae triggered by group A streptococcus (GAS).The basic mechanism of RHD is molecular mimicry in which antigens on GAS stimulates the activation of CD4+ T cells which then cross-react with similar peptides in the heart valve

tissue. According to the Global Burden of Disease (GBD) estimates, 33·4 million cases and 319 400 deaths occurred worldwide in 2015, where maximum mortality was found in low-income and middle-income countries and even in some groups living in high-income countries [1]. The GAS causes pharyngitis and if left untreated or its recurrent infection leads to the rheumatic fever (RF). It is evident that about 0.3 per cent of streptococcal sore throats result in RF and almost 90 per cent of those who get RF develop RHD [2], thus indicating the fact, that there could be influence of genetics, besides molecular mimicry [3] that might affect the development of RHD pathogenesis. However, strong evidence of factors responsible for RHD pathogenicity and the specific triggering events for RHD remain unknown. RHD is a consequence of untreated S. pyogenes mediated autoimmune reactions that leads to extreme valvular damage in genetically susceptible persons [4]. Thus, suggesting that genetic makeup of the individual also contributes in RHD. In this context, polymorphism of various genes related with RHD has also been documented. The present review highlights various genetic susceptibility factors and their role in RHD development, in-order to better understand the disease.

2. Genetic Polymorphism and RHD

The concept of involvement of genetics in RHD pathogenesis develops on the basis of observation that RHD occurs in more than one member in the family of affected person. It indicates the model of inheritance or genetic predisposition of RHD. Many gene polymorphism have been shown to be associated that includes; angiotensin converting enzyme (ACE), Human Leukocytic antigen (HLA), Interleukins (IL) like IL17, transforming growth factor (TGF) beta 1 and Mannan-binding lectin 2 (MBL) [5].

The genetic polymorphism that is most studied in the ACE gene as a marker of functional polymorphism is insertion/deletion (I/D) polymorphism which is attributed by either insertion (I) or deletion (D) of a 287-bp in the intron 16 of the ACE gene [6]. The ACE I/D polymorphism have been linked with an augmented RHD risk in different populations. Morsy et al. [5] have reported an association of DD genotype of ACE gene with the development of RHD in Egyptian children. Similarly, a study from Turkey also found RHD group with more DD genotype in comparison to control group [7]. A study from Saudi Arabia has also reported a significant association of D allele carriage with mitral valve lesion development [8]. Further, a meta-analysis including the studies from countries like India, Turkey, Taiwan and Egypt demonstrated that carriage of D allele was considerably linked with the risk of RHD occurrence [9]. On the contrary, in a Turkish study RHD group contained both II and ID genotype and control group has mainly ID genotype [10]. However, the different observations of these studies may be due to different ethnicity of the participants. Furthermore, within the country a variation in distribution of different allele among different ethnic groups was also observed [11]. These reports clearly put forward that ethnicity must be cautiously taken into consideration that associates ACE-I/D polymorphism with RHD. However, it was hypothesized that ACE I/D polymorphism is associated with RHD severity [12]. All these studies suggested the association of ACE I/D polymorphism with the progression of RHD severity, with a significant role of ACE D allele in RHD progression. Besides ACE I/D polymorphism and other genetic

and environmental factors possibly may also play a significant role in RHD progression [8]. Further, ACE levels are also regulated genetically by I/D gene polymorphisms. D allele was coupled with elevated ACE level in comparison to I allele [8]. Moreover, ACE levels were found to be different in different cells and tissues i.e. elevated ACE levels were present in endothelial cells and heart valves [13]. Thus, the use of inhibitors of ACE might serve as a preventive measure in RHD.

Nevertheless, the control of immune reactions by genetic factors contribute significantly in RHD development. As, immunological responses were mainly controlled by HLA antigens, RHD has been observed to be coupled with HLA antigens [14]. Different hypothesis exists, regarding the association of risk to acquire RHD along with the HLA class II loci. Several reports from various populations have shown the association of HLA alleles with RHD. Guédez et al, [15] showed that definite class II alleles/haplotypes have revealed association with RHD risk and these links may become stronger and more consistent in clinically more homogeneous group of patients [15]. It has also been reported that certain HLA class II alleles i.e. DRB1*07-DQB1*0401-2 and DRB1*07-DQB1*0302 could be associated with the risk of occurring RHD while and certain other alleles of HLA class I i.e. DRB1*06 and DQB1*0602-8, may be protective in RHD. The genetic link between RHD susceptibility and HLA antigens were observed in Turkish patients [14]. Another study on Turkish population demonstrated that RHD susceptibility was related with HLA alleles, for example HLA DQB1*08 influence the occurrence of RHD while HLA-B51, -Cw*4 and -DRB1*01 was found to appear more in control subjects [16]. In addition, another study from same population suggested another allele of HLA (HLA-DRB1*07) as genetically susceptible allele for the development of RHD while a separate allele of HLA (HLA-DRB1*11) may act as a protective allele for RHD [17]. In Indian Population, various studies especially in Kashmiri Muslim patients found that susceptibility to RHD is associated with various HLA-allels and haplotypes. According to this study, HLA-DR4 acts as susceptibility marker for RHD whereas HLA-B5 were present more common in control group [18, 19]. Further, Sreekanth et al., [20] showed HLA DRB1*15 with high RHD risk association in south Indian population. A study in south Indian population suggested the association of +3142 C/C genotype with slight risk for RHD development but it seems to add in severity of disease [21]. Another study from North Indian population showed the association of few HLA-DQB1/DRB1 alleles with RHD [22]. Thus, all these studies have indicated that these gene polymorphism of HLA are associated with RHD.

Further, various studies have suggested that Th17 cell-associated cytokines are involved in RHD pathogenesis [23, 24]. Different gene variants of cytokines are majorly concerned in Th17 response that may be responsible for their differential expression in different individuals. Further, the IL 17 gene polymorphisms are related with a variety of autoimmune and inflammatory diseases development [25]. Espinoza et al. [26] demonstrated that IL17A polymorphism at a particular position (rs2275913) also affects the expression of IL-17A. According to this study, the AA genotype that is more in RHD patients as compared to healthy control leads to increased IL17A level that consequently contributes to autoimmunity in patients with RHD [27]. In another

study of animal models, cells producing IL-17- as well as IL-17 serum levels were notably elevated in rats with RHD than in control rats [24]. Further, IL17F gene polymorphism (rs763780) was also found to be significantly different between RHD patients and healthy controls [27]. Therefore, further studies focusing on expression analysis and genetic polymorphism in large cohort and in different ethnic populations are required for deeply understanding the role of Th17 in RHD pathogenesis.

Transforming growth factor-beta1 gene polymorphism has also been observed in RHD. According to a case control study in Taiwan population, the frequency of CC genotype of TGF-1 509 polymorphism is less in RHD patients in comparison to control subjects [12]. It was also observed that this polymorphism is significantly related with the TGF-1 plasma concentration [28]. The T allele is linked with increased concentration of TGF-1, and this augmentation is more in homozygous genotype for T as compared to heterozygotes. It suggested a dosage effect of the T allele on TGF-1 concentration [29]. Hence, suggesting the protective role of CC genotype of TGF-1 C509T polymorphism in RHD.

Gene polymorphism has also been observed in Ficolin-2 (FCN2) and MBL genes. Three ficolin (FCN) genes namely FCN1, FCN2 and FCN3 are present in humans. These produce ficolin-1, 2 & 3 [30]. It was demonstrated that FCN2 binds with several clinically important pathogens, like Streptococcus *pyogenes* [31]. Several studies have shown that there are various single nucleotide polymorphisms in the promoter region as well as different exons (3, 6 & 8) of the FCN2 gene [32]. Further, alteration in FCN2 serum levels was found to be associated with polymorphisms in FCN2 promoter at -602 and -4 site [33, 34]. A study from Brazalian population demonstrates that haplotype of FCN2 gene promoter affects RHD susceptibility. Another component of the lectin pathway of the complement system is Mannose-binding lectin (MBL) that plays a significant function in innate immune responses, adding in the bacterial clearance. In RHD patients, polymorphisms in MBL2 gene promoter region (-550 H/L, -221X/Y and +4P/Q) as well as in exon 1 (codons 52A/D, 54A/B and 57A/D) were studied [35]. In RHD patients, different alleles of MBL2 gene promoter and exon 1 have been observed [36]. Studies have shown that in the patients with RHD developing mitral stenosis, an association was observed with the A allele at positions (52, 54 and 57). This allele is responsible for over-expression of MBL and is also been found in the majority of patients. The genotypes that are linked with the increased formation of the MBL protein (YA/YA and YA/XA) are found to be present more in acute and chronic carditis patients as compared with the controls [37]. Conversely, O allele at 52, 54 and 57 position, which is linked with low serum levels of MBL showed association with RHD patients with aortic regurgitation [38]. Overall, it is suggested that the MBL2 gene may have an important role in valvular lesions development during RHD. In addition, this study also showed that the genotypes that lead to high serum MBL levels were linked with RHD [39]. It has been observed in several studies that the distribution of alleles, genotypes and haplotypes of MBL2 and FCN2 gene significantly vary among different populations. These variations in genetic patterns of MBL2 and FCN2 may be responsible for altered serum levels of MBL2 and FCN2and hence modulates susceptibility of disease among world populations [40].

3. Conclusion

The present review provided the information on various genetic susceptibly factors involved in the progression of RHD. Current work to elucidate other mechanisms involved in RHD are underway.

The pathogenesis of RHD is not completely known yet, so, a better understanding of RHD pathogenesis will provide the basis of early diagnosis and better treatment options in RHD in near future.

Availability of Data and Material

N/A.

Author's Contribution

SS and AC conceived the idea and designed the framework. SS, drafted the manuscript and wrote first draft. AC provided the critical comments. All authors approved the final version of the manuscript.

Code Availability

N/A.

Funding

N/A.

Compliance with Ethical Standards/Conflicts of Interest/Competing Interests

None.

Ethics Approval

N/A.

Consent to Participate

N/A.

Consent for Publication

N/A.

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