The Heart Matters: Contribution of Genetic Factors in Recurrent Pericarditis

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ABSTRACT: Recurrent pericarditis is a state of repetitive inflammation of the pericardium with intervals of remission. The etiology of recurrent pericarditis is still largely unknown, yet most causes are presumed to be immune mediated. Genetic factors, including human leukocyte antigen (HLA) haplotypes, can be involved in dysregulation of the immune system and as a predisposition to several autoimmune conditions, including recurrent pericarditis. Several diseases are frequently associated with such manifestations. They include systemic lupus erythematosus, familial Mediterranean fever, and tumor necrosis factor receptor-associated periodic syndrome. However, idiopathic recurrent pericarditis remains the most frequently observed clinical condition and the conundrum of this disease still needs to be solved.

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Acute pericarditis accounts for about 5% of emergency room admissions due to chest pain. Of these patients, an estimated 10–30% will develop recurrence of pericarditis within 18 months from the first episode [1,2]. Etiology of recurrence remains mostly obscure, with an estimated 80–90% of cases ascribed to idiopathic recurrent acute pericarditis (IRAP) viral infections. Other prominent causes of recurrent pericarditis include autoimmune diseases, auto-inflammatory diseases, and neoplastic pericarditis [3,4]. Current leading opinions support the notion that IRAP is an immune-mediated process, due to the identification of pro-inflammatory cytokines in pericardial fluid. Further hypotheses suggest a more specific autoimmune pathogenesis, supported by the significant high positivity to anti-nuclear-antibodies (ANA) and the presence of anti-heart and anti-intercalated-disk antibodies in 67.5% of IRAP patients [2,3,5].

Pericarditis is a common manifestation in patients with autoimmune diseases particularly with systemic lupus erythematosus

The prediction of pericarditis relies on a mosaic of factors resembling the mosaic of autoimmunity, quite possibly due to the connection of pericarditis to autoimmunity and auto-inflammation. A possible pivotal piece in this mosaic could be the individual genetic predisposition to the disease. Indeed, familial clustering of pericarditis alludes a plausible genetic connection [3].

GENETIC FACTORS IN IDIOPATHIC RECURRENT ACUTE PERICARDITIS

IRAP is defined as recurrence of pericarditis after a period of at least 6 weeks of complete remission of pericarditis. IRAP is one of the most feared complications of acute pericarditis. The current treatment protocol is composed of a combination of non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine, with glucocorticoids as a second line of treatment. Recent research has shown some new developments, with attempts to treat IRAP with azathioprine, intravenous immunoglobulins (IVIG), and anti-interleukin 1 drugs, with surgical removal of the pericardium considered as a last resort [4].

Scarce data exist with regard to genetic predisposition to IRAP. It has been shown that TNFRSF1A gene SNPs were found in 6% of 131 IRAP patients, providing a new diagnosis and possibly a more appropriate treatment approach [6]. A similar claim was also raised in the case of undiagnosed familial Mediterranean fever patients. This claim was supported by case reports [7], yet a sequencing of 62 IRAP patients failed to reveal MEFV mutations [8].

The idea of genetic contribution to IRAP is also supported by reports of familial clustering of pericarditis. Brucato and Brambilla identified familial cases of IRAP in 6 of 60 patients with IRAP [9].

Specific human leukocyte antigen (HLA) haplotypes have also been described as risk factors for IRAP. Indeed, an association between IRAP was found with the following HLA alleles: HLA-B14, DRB1*01, DQB1*0202, HLA-A*02, and HLA-Cw*07. The association between IRAP and HLA-B DQB1*0202 was confirmed in two different experiments [8,10].

PERICARDITIS, SYSTEMIC LUPUS ERYTHEMATOSUS, AND THE GENETIC BACKGROUND

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with protean manifestations. Also known as "the disease of thousand faces," SLE manifestations are numerous, potentially causing nephritis, skin lesions, serositis (including pericarditis), and neuropsychiatric symptoms [11]. Although the etiology of SLE is not yet clear, a number of factors have been associated with disease development, including exposure to ultraviolet light, changes in hormonal levels [12], and genetic predisposition; composing the mosaic of SLE pathogenesis [11].

Recurrent pericarditis – in all its different forms – is presumed to be mostly immune-mediated

In the past, the pivotal role of genetics in SLE predisposition and phenotypic characterization was highlighted by studies of twins and cases of SLE familial clustering. Based on such studies, concordance rates of SLE in monozygotic twins was found to be about 25%, while dizygotic twin concordance was merely 2%, highlighting the genetic involvement [11]. Currently, most genetic studies focus on genes relating to SLE predisposition, but there are scant data regarding genetic variations and their correlation to specific symptoms such as pericarditis.

A Hungarian group was one of the first to describe a correlation between a specific gene variation and pericarditis in SLE patients [13]. Based on a cohort of 315 SLE patients, Jakab and co-authors [13] found a mutation in the promotor section of the mannose binding lectin (MBL) gene, which is associated with the occurrence of serositis (pericarditis and pleurisy). The mutation causes low serum levels of MBL, a constituent of the innate immune system. Our group [14,15] characterized additional gene variants related to SLE associated pericarditis. Based on an initial cohort of 239 SLE patients, an association was found between TRAF3IP2 gene polymorphisms, coding for Act1, and pericarditis presentation in SLE patients [14]. Furthermore, this association was confirmed in a larger cohort of 315 patients. We further showed that a polymorphism in MIR1279 – rs1463335, which is known to be associated with decreased levels of TRAF3IP2, is also associated with pericarditis [15,16]. Along with these two genes, we investigated other gene polymorphisms, revealing an association between pericardium involvement and following gene variants: PTPN2 – rs2542151 and STAT4 – rs7574865, while a protective association was seen with ATG16L1 – rs2241880. We were even able to build a risk model, including MIR1279, STAT4, TRAF3IP2, and PTPN2 SNPs, explaining about 14% (Cox-Snell R2) of the variability involved in the susceptibility to pericarditis in SLE.

Autoantibodies are frequently found in patients with idiopathic recurrent acute pericarditis

Recently, Li et al. [17] found an additional piece of the mosaic of pericarditis and SLE. The leptin gene, which encodes for a hormone commonly associated with metabolic pathways, was also found to have immune modulating traits. It was found to be associated with pericarditis in SLE patients (specifically, the rs2071045 variant) [17]. Erer and colleagues [18] studied the genes associated with pericarditis manifestation in SLE patients. The group demonstrated a correlation between MEFV gene variations and pericarditis in SLE patients. MEFV mutations are known to cause FMF, an autosomal recessive auto-inflammatory disease, characterized by attack of fever and serositis (including pericarditis) [18]. Hence, this new association between MEFV variations and specific SLE manifestation might gain us a new understanding regarding the pathogenesis of pericarditis.

Last, HLA correlations must also be mentioned. Previous studies have highlighted the DRB1*07 HLA allele as a risk factor for pericarditis in lupus patients, whereas UTR-3 polymorphisms in HLA-G appears to be protective for the pericarditis [19,20].

Interestingly, not only single nucleotide polymorphisms but also variations in the gene copy number can be associated with pericarditis. Indeed, Pereira et al. [21] described an association between the copy number in the C4 gene and pericarditis in juvenile onset SLE. In particular, the copy number of total C4 genes and of C4A alone was significantly lower in patients with pericarditis [21]. Low C4, C4A and C4B gene copy numbers are stronger risk factors for juvenile-onset than for adult-onset SLE. The summary of these associations is shown in Table 1.

PERICARDITIS, FAMILIAL MEDITERRANEAN FEVER, AND THE GENETIC BACKGROUND

FMF is an auto-inflammatory autosomal recessive disease. It is mostly known for the recurrent episodes of inflammation, usually manifesting in the form of fever, serositis (including pericarditis), and synovitis. The disease mainly affects people of Mediterranean descent and is attributed to a defect in the MEFV gene coding for pyrin. Currently, over 310 variants of MEFV have been identified, although the disease is primarily associated with four main mutations [21]. Unfortunately, no data on specific gene polymorphism correlating to the pericarditis phenotype in FMF is up to date. A preliminary correlation was suggested by Kilic and co-authors [22] by an indirect association. In a cohort of 562 patients with FMF, a significant association was found between chest pain and the M694V mutation. Concurrently, out of patients who presented with chest pain, 10.9% were diagnosed with pericar-

Table 1. List of genes associated with pericarditis in systemic lupus erythematosus patients

Gene	Protein	Protein function	Mutations and polymorphisms	SLE risk factor	Remarks	Reference number from the article
MBL	Mannose binding lectin	Carbohydrate recognition and consequent activation of the complement system	Gene promoter – rs7096206; Decreases MBL levels	Yes	MBL high serum levels in SLE patients; low MBL serum levels have been linked to SLE susceptibility	[13,25]
TRAF3IP2	Act1	Signaling adaptor in IL-17 cellular response. Inhibits CD40 and BAFFR signaling	rs33980500 rs13190933 rs13193677	Yes (rs33980500); (rs13193677)	TRAF3IP2 also correlates to psoriatic arthritis and psoriasis	[14]
MIR1279	microRNA		rs1463335	Yes	Decreases TRAF3IP2 levels	[15]
PTPN2			rs242151	No	Association with type I diabetes and Crohn's disease	[15,16]
STAT4	Transcription factor	Mediating response to IL-12 in lymphocyte; regulates differentiation of T helper cells	rs7574865	Yes		[15,16]
ATG16L1		Autophagy	rs2241880	No	Association with a protective effect from pericarditis	[15,16]
LEP	Leptin	Hormone involve in modulation of immune response	rs2071045	No	Increase leptin levels in SLE patients' plasma	[17]
MEFV	Pyrin	Speculated – regulation of inflammasome mediated IL-1β	Exon 10 variations	No	Preliminary results	[18]
C4 and C4A	Complement C4 component	Interaction between the antigen-antibody complex and other complement components	Copy number variations	yes	Lower copies in juvenile SLE patients with pericarditis	

MLB = Mannose-binding lectin, SLE = systemic lupus erythematosus

dial effusion via echocardiography [22]. Clearly these data do not show enough evidence to imply a connection, although one might suggest further research to be conducted.

GENETIC CONTRIBUTION TO PERICARDITIS IN TUMOR NECROSIS FACTOR RECEPTOR ASSOCIATED PERIODIC SYNDROME

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant auto-inflammatory disease considered to be the most prevalent autosomal dominant auto-inflammatory disease. The disease is caused by a mutation in the TNFRSF1A gene, encoding TNF-α. Prominent manifestations of the disease include long-lasting febrile episodes (1–3 weeks), skin rash, arthralgia, myalgia, abdominal pain, conjunctivitis, and serositis. An important distinction should be made between TRAPS and IRAP, since TRAPS responds poorly to colchicine [6,23].

In a cohort of 131 IRAP patients, 6% were found to be carriers of TNFRSF1A mutations [6]. Further analysis of TRAPS patients, carried out to uncover specific gene polymorphism relating to pericarditis, revealed an association with low penetrating TNFRSF1A mutations, also referred as variants of uncertain significance [24].

There is some evidence of associations between genetic variations and the risk of developing pericarditis

DISCUSSION

Recurrent pericarditis can be ascribed to various causes, each one with its own unique features and genetic background. Despite that autoimmune diseases are considered one of the prominent causes of recurrent pericarditis, research on this subject is limited. Autoimmune and auto-inflammatory diseases associated with pericarditis include SLE, rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome, and familial Mediterranean fever; however, research has been conducted mainly on SLE [5]. Distinguishing between different genes related to pericarditis can help to illuminate the different pathogenic processes and possibly pave the way to inform medical choices. These genetic distinctions might be crucial while making treatment choices, such as in the case of TRAPS and colchicine treatment.

Listing all the gene variations raises the question whether a common pathway exists. Current data do not support common genes in the pathogenesis of recurrent pericarditis, although a possible connection between MEFV variations and SLE should be further characterized. The scarcity of genetic data on this pathology shows once again the need to conduct replication studies on large numbers of patients and especially in autoimmune diseases not to neglect the analysis of sub-phenotypes. Furthermore, studies on epigenetic factors underlying this pathology, including miRNA expression levels and methylation status, would be necessary to complete this kind of studies.

Recurrent pericarditis is a general name of a number of different diseases. Each disease has its own genetic predisposition profile to unravel, with SLE genetic connection to pericarditis being the best characterized with eight different genes correlating to pericardial inflammation. Better characterization of the genetic background of pericarditis will possibly lead to a more targeted therapeutic approach.

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References

1. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J* 2015; 36 (42): 2921-64.
2. Schichter-Konfino V, Vadasz Z, Toubi E. Recurrent pericarditis: an autoinflammatory disease? *IMAJ* 2015; 17 (12): 783-4.
3. Maestroni S, Di Corato PR, Cumetti D, et al. Recurrent pericarditis: autoimmune or autoinflammatory? *Autoimmun Rev* 2012; 12 (1): 60-5.
4. Imazio M, Gribaudo E, Gaita F. Recurrent pericarditis. *Prog Cardiovasc Dis* 2016; 59 (4): 1-9.
5. Cantarini L, Lopalco G, Selmi C, et al. Autoimmunity and autoinflammation as the yin and yang of idiopathic recurrent acute pericarditis. *Autoimmun Rev* 2015; 14 (2): 90-7.
6. Cantarini L, Lucherini OM, Brucato A, et al. Clues to detect tumor necrosis factor receptor-associated periodic syndrome (TRAPS) among patients with idiopathic recurrent acute pericarditis: Results of a multicentre study. *Clin Res Cardiol* 2012; 101 (7): 525-31.
7. Yoshioka K, Furumitsu Y, Sano T, Miyamoto T, Agematsu K. Acute pericarditis as the first manifestation of familial Mediterranean fever: a possible relationship with idiopathic recurrent pericarditis. *Intern Med* 2014; 53 (15): 1659-63.
8. Brucato A, Shinar Y, Brambilla G, et al. Idiopathic recurrent acute pericarditis: familial Mediterranean fever mutations and disease evolution in a large cohort of Caucasian patients. *Lupus* 2005; 14 (9): 670-4.
9. Brucato A, Brambilla G. Recurrent idiopathic pericarditis: familial occurrence. *Int J Cardiol* 2005; 102 (3): 529.
10. Lazaros G, Karavidas A, Spyropoulou M, et al. The role of the immunogenetic background in the development and recurrence of acute idiopathic pericarditis. *Cardiology* 2011; 118 (1): 55-62.
11. Kaul A, Gordon C, Crow MK, et al. Systemic lupus erythematosus. *Nat Rev Dis Prim* 2016; 2: 16039.
12. Zandman-Goddard G, Solomon M, Rosman Z, Peeva E, Shoenfeld Y. Environment and lupus-related diseases. *Lupus* 2012; 21 (3): 241-50.
13. Jakab L, Laki J, Sallai K, et al. Association between early onset and organ manifestations of systemic lupus erythematosus (SLE) and a down-regulating promoter polymorphism in the MBL2 gene. *Clin Immunol* 2007; 125 (3): 230-6.
14. Perricone C, Ciccacci C, Ceccarelli F, et al. TRAF3IP2 gene and systemic lupus erythematosus: association with disease susceptibility and pericarditis development. *Immunogenetics* 2013; 65 (10): 703-9.
15. Ciccacci C, Perricone C, Politi C, et al. A polymorphism upstream MIR1279 gene is associated with pericarditis development in systemic lupus erythematosus and contributes to definition of a genetic risk profile for this complication. *Lupus* 2017; 26 (8): 841-8.
16. Ciccacci C, Perricone C, Ceccarelli F, et al. A multilocus genetic study in a cohort of Italian SLE patients confirms the association with STAT4 gene and describes a new association with HCP5 gene. Crispin J, ed. *PLoS One* 2014; 9 (11): e111991.
17. Li H-M, Zhang T-P, Leng R-X, et al. Association of leptin and leptin receptor gene polymorphisms with systemic lupus erythematosus in a Chinese population. *J Cell Mol Med* 2017; 21 (9): 1732-41.
18. Erer B, Cosan F, Oku B, et al. MEFV gene variations in patients with systemic lupus erythematosus. *Mod Rheumatol* 2014; 24 (1): 93-6.
19. Barcat D, Guérin V, Ryman A, et al. Thrombophilia and thrombosis in systemic lupus erythematosus: a case-control study. *Ann Rheum Dis* 2003; 62: 1016-7.
20. Lucena-Silva N, de Souza VSB, Gomes RG, et al. HLA-G 3' Untranslated region polymorphisms are associated with systemic lupus erythematosus in 2 Brazilian populations. *J Rheumatol* 2013; 40 (7): 1104-13.
21. Pereira KM, Faria AG, Liphaus BL, Jesus AA, Silva CA, Carneiro-Sampaio M, Andrade LE. Low C4, C4A and C4B gene copy numbers are stronger risk factors for juvenile-onset than for adult onset systemic lupus erythematosus. *Rheumatology (Oxford)*. 2016; 55 (5): 869-73.
22. Kilic A, Varkal MA, Durmus MS, et al. Relationship between clinical findings and genetic mutations in patients with familial Mediterranean fever. *Pediatr Rheumatol Online J* 2015; 13: 59.
23. Berkun Y, Eisenstein EM. Update on auto-inflammatory diseases and familial Mediterranean fever. *IMAJ* 18 (3-4): 221-4.
24. Cantarini L, Rigante D, Merlini G, et al. The expanding spectrum of low-penetrance TNFRSF1A gene variants in adults presenting with recurrent inflammatory attacks: Clinical manifestations and long-term follow-up. *Semin Arthritis Rheum* 2014; 43 (6):818–23.
25. Panda AK, Parida JR, Tripathy R, Pattanaik SS, Ravindran B, Das BK. Mannose binding lectin: a biomarker of systemic lupus erythematosus disease activity. *Arthritis Res Ther* 2012; 14 (5):R218.

Capsule

Allele-selective transcriptional repression of mutant HTT for the treatment of Huntington's disease

Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder caused by a CAG trinucleotide expansion in the huntingtingene (HTT), which codes for the pathologic mutant HTT (mHTT) protein. Since normal HTT is thought to be important for brain function, **Zeitler** and colleagues engineered zinc finger protein transcription factors (ZFP-TFs) to target the pathogenic CAG repeat and selectively lower mHTT as a therapeutic strategy. Using patient-derived fibroblasts and neurons, the authors demonstrated that ZFP-TFs selectively repress › 99% of HD-causing alleles over a wide dose range while preserving expression of › 86% of normal alleles. Other CAG-containing genes are minimally affected, and virally delivered ZFP-TFs are active and well tolerated in HD neurons beyond 100 days in culture and for at least 9 months in the mouse brain. Using three HD mouse models, the authors demonstrated improvements in a range of molecular, histopathological, electrophysiological, and functional endpoints. These findings support the continued development of an allele-selective ZFP-TF for the treatment of HD.

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Eitan Israeli

"Imagination is the source of every form of human achievement. And it's the one thing that I believe we are systematically jeopardizing in the way we educate our children and ourselves"

Sir Ken Robinson (born 1950), English expert on innovation in education