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BRIEF REPORT

Genetic Determinants in Hepatitis C Virus–Associated Mixed Cryoglobulinemia: Role of Polymorphic Variants of BAFF Promoter and Fcγ Receptors

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Objective. **Mixed cryoglobulinemia (MC) is a hepatitis C virus (HCV)–related immune complex disorder. Only some HCV-infected patients develop MC, which suggests that the genetic background of the host plays a key role. This study was undertaken to evaluate the contribution of host genetic factors in the pathogenesis of HCV-associated MC (HCV-MC) by analyzing allelic variants of low-affinity Fcγ receptor (FcγR) genes and BAFF promoter.**

Methods. **FcγR polymorphisms (*FCGR2A* 131 R/H, *FCGR2B* 232 I/T, *FCGR3A* 176 V/F, and *FCGR3B* NA1/NA2) and BAFF promoter polymorphism −871 C/T were analyzed in 102 patients with HCV-MC and 108 patients with HCV without MC, using polymerase chain reaction–based techniques.**

Results. **A higher prevalence of −871 T/T homozygosity (31% versus 16%; $P = 0.001$) and a greater frequency of T alleles of the BAFF promoter (80% versus 57%; $P = 0.004$) were found in the HCV-MC group than in the HCV group. A significant increase in serum BAFF concentration was significantly associated with the higher frequency of the T allele in HCV-MC (mean ± SD 4.12 ± 1.29 versus 2.09 ± 0.81 ng/ml; $P < 0.0005$). The distribution of the FcγR genotypes was not significantly different. In the 21 HCV-MC patients treated with rituximab, the response was strictly related to F allele homozygosity (significantly reduced in 5 of 5 patients with the *FCGR3A* F/F genotype versus 4 of 16 with V/V or V/F; $P < 0.0005$).**

Conclusion. **These results indicate the importance of host genetic background in the development of HCV-MC, suggesting that mechanisms enhancing Ig production and B cell survival may play a relevant role. Genetic FcγR variants seem to be crucial to the effectiveness of rituximab therapy.**

Hepatitis C virus (HCV) infection is characterized by a variety of extrahepatic manifestations. Its association with mixed cryoglobulinemia (MC), a lymphoproliferative/autoimmune disorder, is unquestioned today. MC is characterized by the presence of circulating immune complexes called cryoglobulins in the peripheral blood and, although benign, is considered a step predisposing to lymphoma. Approximately 40–60% of patients infected with HCV develop MC (1). Their symptoms can be described as different consequences of a systemic small-vessel vasculitis due to precipitation and deposit of the immune complexes on vascular endothelium (1). The reason only some HCV-infected patients develop MC is still unknown and is therefore a topic for research. Several different approaches have been used in an attempt to determine whether the ability to predispose to MC depends on viral or host factors. Recent studies have failed to identify specific viral features associated with MC (2), which suggests that the host's genetic substrate plays a major role in determining the susceptibility to MC observed in some patients with HCV.

MC is characterized by the abnormal presence of large immune complexes, which may be due to two not mutually exclusive phenomena: reduced uptake and

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clearance of Ig by macrophages of the reticuloendothelial system and excessive production/secretion of Ig by B cells.

An essential role in Ig clearance is played by Fcγ receptors (FcγR). These receptors differ in antibody affinities depending on their molecular structure, which allows activation of FcγR type I (FcγRI) by a monomeric IgG (high affinity), while FcγRII and FcγRIII must bind multiple IgG molecules within an immune complex to be activated (low affinity) (3). The clearance of circulating cryoglobulins is mainly mediated by low-affinity FcγR. These receptors are present on leukocytes (mainly on phagocytes) and contribute to regulating recruitment to inflammatory lesions, phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), release of mediators of inflammation, and regulation of B cell activation (3).

The control of these essential functions of the immune response arises from a finely tuned balance of activating receptors (FcγRIIa, FcγRIIIa, and FcγRIIIb) and inhibitory receptors (FcγRIIb); in fact, perturbations in FcγR function result in susceptibility to infection or autoimmunity (e.g., rheumatoid arthritis [RA], systemic lupus erythematosus [SLE], myasthenia gravis, Guillain-Barré syndrome, Wegener's granulomatosis, and multiple sclerosis) (3). Single-nucleotide polymorphisms (SNPs) affecting IgG-binding affinities have been described for FcγRIIa (*FCGR2A* R131H), FcγRIIb (*FCGR2B* I232T), and FcγRIIIa (*FCGR3A* V176F), while FcγRIIIb has 2 isoforms, called NA1 and NA2, that differ by 4 amino acids and glycosylation sites.

As previously stated, MC is characterized by mono-oligoclonal expansion of B lymphocytes with abnormal production of cryoglobulins. Recent studies have shown high levels of a B cell–specific cytokine, namely BAFF (or B lymphocyte stimulator), in the serum of HCV patients with MC (for review, see ref. 4). BAFF, a tumor necrosis factor α (TNFα) family member, is a key regulator of B cell differentiation, survival, and Ig secretion, and alterations in its expression have been initially associated with different autoimmune disorders, such as Sjögren's syndrome, SLE, and RA (5). Overexpression of BAFF in monocytes has been associated with the presence of a T allele at the polymorphic site −871 C/T of its promoter in patients with RA and familial lymphoproliferative disorders (6).

Therefore, since no data are available on this topic, we decided to investigate the role of polymorphic variants of genes involved in the clearing of cryoglobulins (low-affinity *FCGR* genes) as well as genes responsible for cryoglobulin production and B cell expansion (BAFF), with the aim of defining potential genetic profiles characteristic of the cryoglobulinemic phenotype. The identification of a particular genetic substrate predisposing to MC may lead to the identification of new and effective therapeutic targets.

PATIENTS AND METHODS

Patients. We studied 210 HCV patients: 102 with HCV-MC and 108 chronic HCV carriers without any evidence of serum cryoglobulins or autoimmune/lymphoproliferative disorders. Patients were consecutively recruited at the Department of Internal Medicine, Center for Systemic Manifestations of Hepatitis Viruses of the University of Florence. Diagnostic criteria for MC and clinical details for the patients with MC are available online at http://www.unifi.it/masve/Supplementary_Materials.pdf. Of the 102 patients with HCV-MC, 21 underwent rituximab therapy due to the presence of contraindications or a lack of response to antiviral treatment. (Data are available online at http://www.unifi.it/masve/Supplementary_Materials.pdf.)

Cell isolation and culture. Peripheral blood mononuclear cells were isolated from fresh anticoagulated blood by gradient precipitation on Lymphoprep according to the recommendations of the manufacturer (Axis-Shield). After the second wash, the cells were counted and stored at −80°C.

DNA extraction. Genomic DNA was extracted using QIAamp DNA Mini Kit according to the recommendations of the manufacturer (Qiagen).

FcγR genotyping. *FCGR2A* genotyping was performed using a specific TaqMan SNP Genotyping Assay (rs1801274; Applied Biosystems) with supplied probes and primers on a Rotor Gene 6000 (Corbett Research). *FCGR2B* genotyping was carried out using oligonucleotide probing based on fluorescence resonance energy transfer technology, as previously described (7). Genotyping of *FCGR3A* 158 V/F polymorphism was performed using a specific TaqMan SNP Genotyping Assay (rs396991). Genotyping of *FCGR3B* consisted of an allele-specific polymerase chain reaction (PCR) performed according to the method of Biezeveld et al (8).

Human BAFF and APRIL enzyme-linked immunosorbent assay (ELISA). Serum levels of human BAFF and APRIL were determined using Quantikine BAFF Immunoassay (R&D Systems Europe) and human APRIL ELISA (Bender MedSystems) according to the recommendations of the manufacturer.

BAFF promoter polymorphism genotyping. We performed restriction fragment length polymorphism analysis to evaluate the BAFF promoter genotype. The primers used for BAFF promoter amplification were 5′-GGCACAGTCAACATGGGAGT-3′ (forward) and 5′-GCTAAGTGTTTTAGCATTGAATTG-3′ (reverse) as previously described (6). The PCR products were subjected to a restriction enzyme–based screening of the −871 C/T using 20 units of *Bsr* BI restriction enzyme.

Table 1. Main clinical characteristics and laboratory data on the 210 patients with HCV or with HCV-MC*

	HCV (n = 108)	HCV-MC (n = 102)	*P*
Age, years	57.4 ± 23.8	59.6 ± 26.1	NS
Sex, no. male/no. female	72/36	39/63	<0.0005
Histologic features, no. of patients			NS
Chronic hepatitis	86	84	
Cirrhosis	22	18	
ALT, × ULN	3.72 ± 2.5	3.23 ± 2.1	NS
Viral titer, IU/ml × 10^6	2.3 ± 2.9	1.9 ± 1.72	NS
HCV genotype, no. (%)			NS
1	66 (61)	58 (57)	
2	23 (21)	29 (28)	
3	14 (13)	12 (12)	
4	5 (5)	3 (3)	
Cryocrit, %	0	7.1 ± 6.1	<0.0005
C3, mg/dl (normal 83–177)	113.3 ± 63.8	124.5 ± 60.6	NS
C4, mg/dl (normal 20–150)	87.6 ± 44.3	14.1 ± 12.4	<0.0005
RF, IU/ml (normal <25)	15.7 ± 7.4	443.5 ± 205.4	<0.0005

* Except where indicated otherwise, values are the mean ± SD. HCV-MC = hepatitis C virus–associated mixed cryoglobulinemia; NS = not significant; ALT = alanine aminotransferase; ULN = upper limit of normal; RF = rheumatoid factor.

Criteria for rituximab response determination. The 21 patients who underwent rituximab therapy were administered 4 weekly injections of 375 mg/m^2 and followed up as previously described (9). Overall, a complete clinical response was defined as improvement in all baseline clinical MC manifestations, while a partial response was defined as improvement in at least half of the baseline clinical symptoms. All other patients were classified as clinical nonresponders (9).

Statistical analysis. Data are expressed as the mean ± SD. Comparisons between quantitative variables in the 2 patient groups were analyzed using Student's unpaired *t*-test and the unpaired Wilcoxon test when necessary, whereas the categorical variables (the genotype distribution for the low-affinity FcγR and the distribution of the −871 C/T alleles of the BAFF promoter) were analyzed using Pearson's chi-square test and Fisher's exact test when necessary. All tests were 2-sided, and *P* values less than 0.05 were considered significant. Analyses were performed using Stata version 9.0 statistical software (StataCorp).

The biologic samples obtained from the patients in each study group were coded, and laboratory personnel were blinded with regard to the code. For the genotyping analysis,

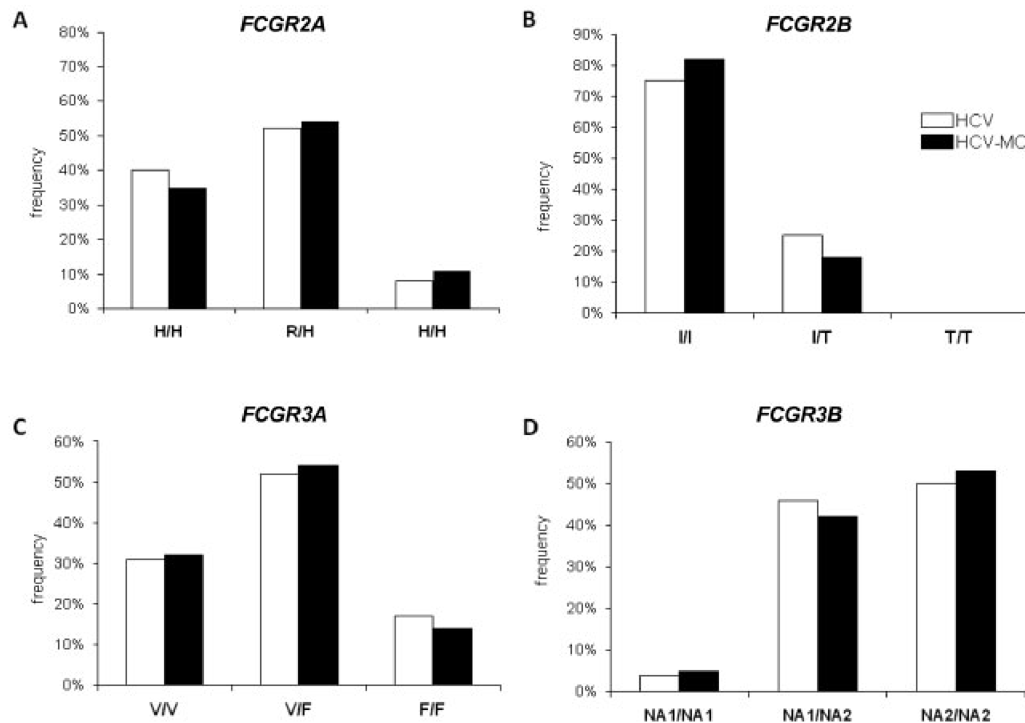

Figure 1. Analysis of allele distribution for *FCGR2A* (**A**), *FCGR2B* (**B**), *FCGR3A* (**C**), and *FCGR3B* (**D**) in patients with hepatitis C virus–associated mixed cryoglobulinemia (HCV-MC) and patients with HCV without MC.

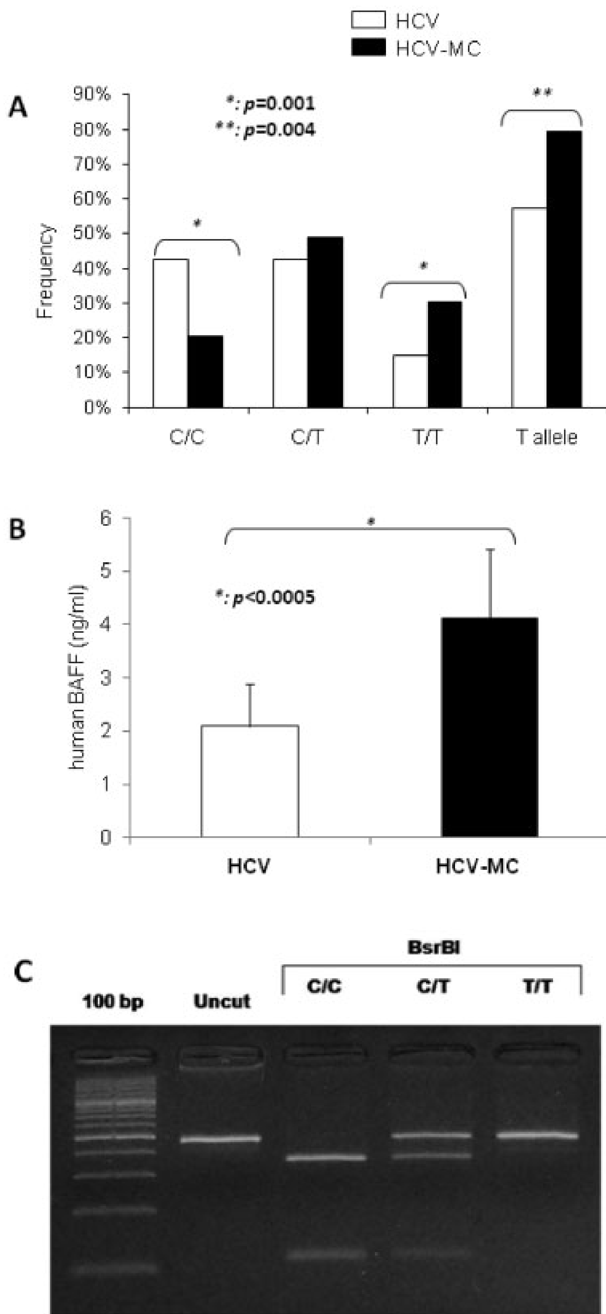

Figure 2. A, Analysis of allele distribution for the −871 BAFF promoter polymorphism in patients with HCV-MC and patients with HCV without MC. **B**, Serum BAFF levels in patients with HCV-MC and patients with HCV without MC. **C**, Representative results of −871 C/T BAFF promoter genotyping. A 100-bp MW marker, undigested polymerase chain reaction product (uncut; 468 bp), and amplicons digested with *Bsr* BI restriction enzyme are shown. Homozygous C/C was cleaved in 2 fragments (116 bp and 352 bp). For C/T, the presence of 3 bands (468 bp, 352 bp, and 116 bp) indicated heterozygosity. A single uncut band (468 bp) indicated T/T homozygosity. See Figure 1 for other definitions.

amplicon sequencing was used to validate each technique used. All genotyping results were consistent with Hardy-Weinberg equilibrium.

RESULTS

Patient characteristics. The main clinical and laboratory characteristics of the 210 HCV patients with or without MC who were evaluated in this study are summarized in Table 1. No significant differences were observed regarding age, severity of liver disease, viremia titers, or viral genotype distribution. As expected, the HCV-MC group had significantly more women ($P < 0.0005$), as well as higher cryoglobulin levels ($P < 0.0005$), higher levels of rheumatoid factor ($P < 0.0005$), and lower levels of C4 ($P < 0.0005$) than the HCV group, confirming the quality of patient recruitment. A description of MC symptom distribution in HCV-MC patients and a detailed list of patient characteristics before treatment and during a 6-month followup period for the 21 patients treated with rituximab are available online at http://www.unifi.it/masve/Supplementary_Materials.pdf.

FcγR polymorphisms. The results of the analysis of the genotype distribution for the low-affinity FcγR in the HCV and HCV-MC groups are summarized in Figure 1. We did not find any significant difference in the distribution of the polymorphic variants for *FCGR2A* 131 R/H (Figure 1A), *FCGR2B* 232 I/T (Figure 1B), *FCGR3A* 158 V/F (Figure 1C), or *FCGR3B* NA1/2 (Figure 1D) in the 2 populations of patients studied.

Twenty-one patients in the HCV-MC group were treated with anti-CD20 antibodies (rituximab) for severe MC. Interestingly, analysis of clinical and biohumoral parameters in all 5 patients bearing an *FCGR3A* 158 F/F genotype indicated reduced response to rituximab (no response in 4 patients [patients 1, 3, 10, and 18] and partial response in 1 patient [patient 13]), while the V/V and V/F genotypes were associated with a complete response to the therapy in 12 patients (patients 2, 5, 6, 8, 9, 11, 14, 15, 17, 19, 20, and 21), a partial response in 3 (patients 7, 12, and 16), and absence of response in the remaining patient (patient 4). The association between the presence of a homozygous *FCGR3A* 158 F/F genotype and a reduced or absent response to rituximab therapy was highly statistically significant (reduced response in 5 of 5 patients with the F/F genotype versus 4 of 16 patients with the V/V or V/F genotype; $P < 0.0005$).

BAFF promoter polymorphism. The analysis of the distribution of the −871 C/T alleles of the BAFF promoter revealed a significantly higher prevalence of T allele homozygosity in the group of patients with MC than in the group of HCV patients without MC (31% versus 16%; $P = 0.001$) (Figure 2A), paralleled by a significant reduction in the frequency of the C/C genotype in the group of patients with MC in comparison to HCV patients without MC (21% versus 46%; $P = 0.001$). In addition, the T allele (homozygous T/T plus heterozygous T/C) was significantly more prevalent in HCV-MC patients when compared to HCV carriers without MC (80% versus 57%; $P = 0.004$). The higher frequency of the T allele in the HCV-MC group was associated with a significant increase in serum BAFF levels, when compared to HCV patients without MC (mean ± SD 4.12 ± 1.29 versus 2.09 ± 0.81 ng/ml; $P < 0.0005$) (Figure 2B). In contrast, the analysis of serum APRIL levels in the HCV and HCV-MC populations did not show any significant difference. (Data are available online at http://www.unifi.it/masve/Supplementary_Materials.pdf.)

DISCUSSION

Although several mechanisms involved in the pathogenesis of HCV-MC have been proposed, the reasons cryoglobulins appear in only half of all HCV patients are still unclear. In the present study, the potential contribution of some host genetic determinants to the pathogenesis of HCV-MC was evaluated. This is the first study to explore the possibility that the presence of SNPs that reduce the affinity of FcγR alters the main mechanisms involved in cryoglobulin clearance in HCV patients. Furthermore, this is the first study to demonstrate a significant association between MC phenotype, strong BAFF expression, and a specific BAFF promoter genotype.

The results of the screening of the 4 major types of low-affinity FcγR in a large population of HCV patients with and without MC showed a similar prevalence of allele distribution in both populations, suggesting that accumulation of immune complexes in HCV-MC is not caused by an impaired clearance capacity by phagocytes of the reticuloendothelial system secondary to the reduced affinity of some polymorphic variants of FcγR. Conversely, in RA, another autoimmune disorder that shares some features with MC, some studies have associated the higher-affinity allele *FCGR3A* 158V with susceptibility to the disease or with more severe forms (for review, see ref. 3). In this context, our data underline a difference between the pathogenetic mechanisms driving HCV-MC and other autoimmune disorders.

Interestingly, analysis of a cohort of patients treated with anti-CD20 antibodies for MC revealed the importance of the allelic status of the *FCGR3A* 158 V/F polymorphism. In fact, although the number of patients with a homozygous F/F genotype was low, a diminished response to the biologic therapy was evident in all cases. The primary role in ADCC played by low-affinity FcγR can possibly explain this phenomenon. However, discordant results with regard to the effects of *FCGR3A* allelic variants in determining the response to biologic agents have been reported, underlying the absence of a general unspecific effect for all types of diseases treated with biologic agents. In particular, a worse response to biologic therapies in patients with an *FCGR3A* 158 F/F genotype was previously suggested in the treatment of non-Hodgkin's lymphoma (NHL) (10) and Crohn's disease (11). Conversely, the role of the *FCGR3A* polymorphism seems to be less relevant in the biologic treatment of chronic lymphocytic leukemia, suggesting potential divergent mechanisms of action between these diseases (12). Although a limited number of cases were examined, our data provide, for the first time, information concerning the influence of the *FCGR3A* genotype on rituximab treatment in subjects with HCV-MC. These results become more important when considering the increasing and successful use of anti-CD20 therapy in MC (for review, see ref. 1).

In addition, recent studies have proposed a reduced dose of rituximab for patients with MC compared to those with NHL (13). In this light, although definitive evidence of a direct relationship between rituximab dose, clinical response, and *FCGR3A* genotype has not yet been provided in the case of patients with HCV-MC, the *FCGR3A* genotype could be useful in tailoring the rituximab dose in MC patients, which would reduce side effects and lower the (high) cost of therapy. In vitro data demonstrating the influence of *FCGR3A* polymorphism on the concentration–effect relationship of rituximab support this hypothesis (14). A dedicated study of a larger population of HCV-MC patients treated with rituximab is already ongoing in our center.

The expansion of rheumatoid factor–producing B cell populations and the abnormal production of Ig are the main features of MC. High levels of serum B cell–specific cytokines are involved in the pathogenesis of the disease (for review, see ref. 4), but the mechanisms underlying this phenomenon are largely unknown. In the present study, we confirm the high serum BAFF concentration in MC patients. Furthermore, we investigated the serum levels of another B cell–

specific TNFα family member, APRIL, which shares several biologic characteristics with BAFF, including a cell receptor. The analysis of serum APRIL levels in HCV and HCV-MC populations did not show any significant difference, corroborating the specificity of the results obtained for BAFF.

We then tried to explain the mechanism/s underlying the data obtained. We showed that the presence of a particular polymorphic variant of the BAFF promoter was strongly associated with the presence of MC and elevated serum BAFF levels, emphasizing the potential contribution of the genetic background of HCV-infected patients in the development of lymphoproliferative disorders. Consistent with these findings, specific HLA clusters have recently been associated with a higher risk of developing MC syndrome and concomitant NHL (15). In addition, findings showing a limited importance of virus-specific determinants are consistent with the relevance of genetic host factors in promoting HCV-related lymphoproliferative disorders (2).

The data concerning BAFF overexpression in MC patients can have immediate transferability to clinical practice since anti-BAFF monoclonal antibody (belimumab) is already in phase III clinical testing for SLE treatment, with encouraging results. The use of belimumab to treat patients with HCV-MC could be envisaged after appropriate clinical trials.

A major limitation in genetic studies is the sample size, especially when dealing with rare disorders like MC, where the analysis of a consistent number of well-characterized cases is sometimes difficult. Although the populations in the present study were sufficiently large for a correct statistical analysis (102 patients with HCV-MC versus 108 patients with HCV), a multicenter study of a larger cohort of patients is needed to validate the present results.

In conclusion, the transcriptional activation induced by the particular allelic variant of BAFF promoter can be considered one of the mechanisms contributing to the pathogenesis of HCV-related autoimmune/lymphoproliferative disorders. This polymorphism can contribute, possibly in combination with other allelic patterns, to determining a genetic profile characteristic of the cryoglobulinemic phenotype.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Zignego had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Gragnani, Piluso, Giannini, Caini, Petrarca, Laffi, Zignego.

Acquisition of data. Gragnani, Piluso, Giannini, Caini, Fognani, Monti, Ranieri, Razzolini, Froio.

Analysis and interpretation of data. Gragnani, Piluso, Giannini, Caini, Fognani, Monti, Petrarca, Ranieri, Razzolini, Froio, Laffi, Zignego.

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