Research Article

Inherited Variation in Cytokine, Acute Phase Response, and Calcium Metabolism Genes Affects Susceptibility to Infective Endocarditis

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Infective endocarditis (IE) is a septic inflammation of the endocardium. Recognition of microbial patterns, cytokine and acute phase responses, hemostasis features, and alterations in plasma lipid and calcium profile all have been reported to affect pathogenesis and clinical course of IE. Having recruited 123 patients with IE and 300 age-, sex-, and ethnicity-matched healthy blood donors, we profiled their genomic DNA for 35 functionally significant polymorphisms within the 22 selected genes involved in the abovementioned pathways, with the further genetic association analysis. We found that the G/A genotype of the rs1143634 polymorphism within the IL1B gene, the G/T genotype of the rs3212227 polymorphism within the IL12B gene, the A/G genotype of the rs1130864 polymorphism within the CRP gene, and the G allele of the rs1801197 polymorphism within the CALCR gene were associated with a decreased risk of IE whereas the T/T genotype of the rs1205 polymorphism within the CRP gene was associated with a higher risk of IE. Furthermore, heterozygous genotypes of the rs1143634 and rs3212227 polymorphisms were associated with the higher plasma levels of IL-1β and IL-12, respectively. Our results indicate that inherited variation in the cytokine, acute phase response, and calcium metabolism pathways may be linked to IE.

1. Introduction

Infective endocarditis (IE) is defined as an infection of the endocardial surface, which may involve native or prosthetic heart valves, the mural endocardium, interventricular septum, chordae tendineae, or surfaces of intracardiac devices [1]. In general, IE is caused by bacteria, in particular Staphylococcus, Streptococcus, and Enterococcus spp. [2], but fungi have also been reported as a culprit [3]. The most common signs and symptoms of IE are malaise, fatigue, coughing, chills, fever, weight loss, and heart murmur [1]. Incidence of IE significantly varies in different countries (from 1.5/100,000 in Netherlands to 11.6/100,000 in United States), with an average case fatality rate of 25% [4]. However, case fatality rates considerably depend on the etiological agent: from 10% in patients infected with Streptococcus spp. to 40% in those infected with Staphylococcus aureus [5–9]. The development and course of IE may depend on (1) the recognition of pathogen-associated molecular patterns as well as cytokine and acute phase response to causative agents [10–12], (2) hemostasis [13–15], (3) plasma lipid profile [16, 17], and (4) plasma calcium profile [18, 19].

Progress in genotyping technologies reasoned the studies on the association of single nucleotide polymorphisms
(SNPs) with human diseases [20]. SNPs located in different genomic regions may cause distinct consequences, including altered (1) transcription initiation; (2) mRNA splicing; (3) protein folding, stability, and expression; and (4) posttranslational modifications [21]. Previously, we reported that the C/C genotype of the rs3775073 polymorphism within the gene is associated with a twofold decreased risk of IE; other polymorphisms within the genes encoding pattern recognition receptors did not show a predictive value. Here, we investigated whether the SNPs within the cytokine, acute phase response, lipid metabolism, and calcium metabolism genes can alter individual susceptibility to IE.

2. Materials and Methods

2.1. Population. Inclusion criteria were as follows: (1) living in Kemerovo region for ≥2 generations; (2) Russian ethnicity; (3) clinically (modified Duke criteria, at least 1 major and 1 minor criteria or 3 minor criteria being fulfilled [22]) and histologically verified diagnosis of IE; and (4) written informed consent. Exclusion criteria were as follows: (1) belonging to the immigrant or aboriginal populations, (2) previous cancer diagnosis, (3) concomitant mental disorders and/or autoimmune diseases, (4) drug addiction, and (5) refusal to sign a written informed consent. All the patients underwent antibiotic therapy in the acute phase during the first admission to their district hospital according to the European guidelines [22]. Antibiotic therapy and treatment of all concomitant diseases were further performed during the preoperative period at the Kemerovo Cardiology Centre.

In total, we recruited 161 patients with IE admitted to our Research Institute during 2009–2016. After exclusion of 38 patients due to the abovementioned criteria, the study group finally included 123 patients (Table 1). The control group for this study was formed from 300 age- and sex-, and ethnicity-matched asymptomatic blood donors with no history of drug addiction, cardiovascular disease, cancer, and autoimmune and mental disorders (Table 1). Data on the clinicopathological features and hospital complications/case fatality rate of patients with IE are presented in Table 2.

2.2. SNP Selection and Genotyping. For this study, we defined four main criteria for SNP selection: (1) location within cytokine, acute phase response, hemostasis, lipid metabolism, or calcium metabolism genes; (2) minor allele frequency ≥5% for Russian population tested with HapMap; (3) functional alteration of protein expression; and (4) few or no studies investigating the role of an SNP in IE. The National Center for Biotechnology Information dbSNP, SNPinfo, and SNPnexus databases were utilized for the SNP selection [23, 24]. In total, we selected 35 SNPs within 22 genes (Table 3).

The procedures of DNA extraction and genotyping were the same as previously described [12, 25–27]. Briefly, 5 mL of venous blood was collected into a tube with ethylenediaminetetraacetic acid. Then, 0.5 mL of blood was mixed with 1 mL of saline-sodium citrate buffer (Promega) following centrifugation at 12,000 rpm for 2 min. The pellet was digested in a mixture of 10% sodium dodecyl sulfate (Sigma) with 100 µg/mL proteinase K (Helicon) for 3 h at 50°C. Upon digestion, we added phenol:chloroform:isoamyl alcohol (25:24:1) to the lysate, vortexed it for 20 seconds, and centrifuged at 12,000 rpm for 15 min; 70% ethanol was further utilized to precipitate genomic DNA from a viscous interphase layer. The sample was finally centrifuged at 12,000 rpm for 5 min. DNA pellet was incubated overnight in deionized water at room temperature and was further stored at −70°C until use.

Genotyping was carried out in a 96-well format using the TaqMan SNP assay on the ViiA™ 7 Real-Time PCR System (Life Technologies) according to the manufacturer’s instructions. Amplification mixture contained 100 ng of DNA, 1.25 µL of each primer, 2.5 mM of MgCl2, 1 mM of dNTPs, and 1 U of Taq polymerase (Life Technologies), in a total volume of 10 µL. We employed the following polymerase chain reaction (PCR) protocol: hold stage 50°C for 120 s and 95°C for 10 min and PCR stage 95°C for 15 s and 60°C for 1 min repeated in 40 cycles. Table 3 demonstrates the sequence-specific primers for the genotyped SNPs. Laboratory staff was blinded to patient status, and one-tenth of the samples was repeatedly genotyped for quality control purposes. The study workflow is summarized in Figure 1.

2.3. Measurement of Plasma Cytokine Level. Venous blood was withdrawn during hospital admission and 7 days post-operation. The plasma was obtained with a centrifugation for 15 min at 1780 × g and −4°C; 300 µL aliquots have been stored at −80°C until use. The plasma levels of interleukin-1β, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor (TNF-) α, and C-reactive protein (CRP) were measured by enzyme-linked immunosorbent assay using the kits purchased from eBioscience (BMS224/2, BMS213/2, BMS204/3CE, BMS215/2, BMS238CE, BMS223/4CE, and 88-7502-

Table 1: Characteristics of the study population.

|                  | Controls | Cases | Total    | p value |
|------------------|----------|-------|----------|---------|
| Number of subjects | 300 (70.92%) | 123 (29.07%) | 423 (100.00%) |         |
| Median age with 95% CI | 55.00 (53.00–56.00) | 50.00 (48.00–53.00) | 53.00 (52.00–55.00) | 0.12   |
| Interquartile range | 44–62 | 37–59 | 42–61 |         |
| Males | 190 (63.00%) | 77 (63.00%) | 267 (63.12%) | 0.99   |
| Females | 110 (37.00%) | 46 (37.00%) | 156 (36.88%) |         |

CI: confidence interval.
28, resp.) according to the manufacturer’s instructions. All samples were plated in duplicates, with average concentrations used for further analysis.

2.4. Statistical Analysis. The statistical analysis was performed as in [12, 25–27] using GraphPad Prism (GraphPad Software) and SNPStats, a web tool for the analysis of genetic association studies [28].

3. Results

Here, we evaluated the distribution of SNPs within 22 core genes involved in cytokine activity, acute phase response, lipid metabolism, and calcium metabolism genes in a sample of 123 patients with IE and 300 matched asymptomatic control individuals (Table 3). Tables 1 and 2 summarize demographic and clinicopathological characteristics of cases and controls. We did not find statistically significant gender differences between the groups (Table 1). The genotype distributions in both groups are presented in Table 4. All the genotype distributions were in Hardy-Weinberg equilibrium that confirmed a good quality of the genotyping.

We first asked whether an inherited variation within the genes encoding cytokines and acute phase proteins may play a role in the risk of IE development. Having performed the genetic association analysis with the adjustments for age and gender, we found that the G/A genotype of the rs1143634 polymorphism within the IL1B gene was associated with a lower risk of IE (OR = 0.43, 95% CI = 0.26–0.71, p = 0.0016, overdominant model, Table 4). Similarly, the G/T genotype of the rs3212227 polymorphism within the IL12B gene correlated with a decreased risk of IE (OR = 0.57, 95% CI = 0.34–0.94, p = 0.0250, overdominant model, Table 4). Finally, we observed that the A/G genotype of the rs1130864 polymorphism within the CRP gene was also associated with a lower risk of IE (OR = 0.54, 95% CI = 0.34–0.86, p = 0.0083, overdominant model, Table 4). Conversely, the T/T genotype of the rs1205 polymorphism within the CRP gene was associated with a higher risk of IE (OR = 2.42, 95% CI = 1.32–4.43, p = 0.0047 according to a recessive model, Table 4). Other SNPs were not significantly different between cases and controls (Table 4).

We further investigated whether the inherited variation in the pathways of hemostasis, lipid metabolism, and calcium metabolism can be linked to IE. The A/G genotype of the
| Single nucleotide polymorphism | Nucleotide substitution | Chromosomal position | Amino acid substitution | Forward 5'-3' and reverse 3'-5' polymerase chain reaction primers |
|--------------------------------|------------------------|----------------------|------------------------|---------------------------------------------|
| **IL1B gene**                 |                        |                      |                        |                                             |
| rs1143634                     | G > A                  | 113590390            | Phe105Phe              | F: ctaagctctgttatcccaagtgtgtc               |
|                               |                        |                      |                        | R: aagaagatagttgtaaagtgtgga               |
| **IL6 gene**                  |                        |                      |                        |                                             |
| rs1554606                     | T > G                  | 22768707             | Intronic               | F: ttagtctctctgggaaaggtactc               |
|                               |                        |                      |                        | R: caggcctctctctctctctgtgc               |
| rs1800796                     | G > C                  | 22766246             | 5'-upstream            | F: atggccaggcagttctacaacagcc               |
|                               |                        |                      |                        | R: ctcacaggagacgagccaacacacag             |
| rs2069827                     | G > T                  | 22765456             | 5'-upstream            | F: gcaccaacagagtcagtttatttc               |
|                               |                        |                      |                        | R: acttgtgaagatctctctctgtca               |
| **IL6R gene**                 |                        |                      |                        |                                             |
| rs2228145                     | A > T/C                | 154426970            | Asp358Val/Ala          | F: satttttttttaactctgtcag                   |
|                               |                        |                      |                        | R: tctctctctacacsactccaccc                 |
| rs2229238                     | T > C                  | 154437896            | 3'-UTR                 | F: ccaacagcctggaacctgtgtgatga             |
|                               |                        |                      |                        | R: aacaacaacaggggtgctcagaaaaag             |
| **IL8 gene**                  |                        |                      |                        |                                             |
| rs2227306                     | C > T                  | 74607055             | Intronic               | F: aactctaaacttattatagga                   |
|                               |                        |                      |                        | R: gtcacagtgtgctgtagctgt                 |
| **IL10 gene**                 |                        |                      |                        |                                             |
| rs1800871                     | A > G                  | 206946634            | 5'-upstream            | F: agttgacaaactgtagcagcagagat             |
|                               |                        |                      |                        | R: ttatccacactgtaacaggggtacac             |
| rs1800872                     | T > G                  | 206946407            | 5'-upstream            | F: ttctttttttcagctgctttcctctactacg        |
|                               |                        |                      |                        | R: acaggccgggccagagattgtgctgcaggc       |
| rs1800896                     | T > C                  | 206946897            | 5'-upstream            | F: tctctctctatcactctctctgcc               |
|                               |                        |                      |                        | R: tcccaagaacgcttagtaggtgtg           |
| **IL12B gene**                |                        |                      |                        |                                             |
| rs3212227                     | T > G                  | 158742950            | 3'-UTR                 | F: attttttagaatggacatgtaggtc               |
|                               |                        |                      |                        | R: aactatatagatactcagagacctgat             |
| **IL12RB gene**               |                        |                      |                        |                                             |
| rs375947                      | A > G                  | 18180451             | Met365Thr              | F: aggtctgctctattctgaatagtgtc             |
|                               |                        |                      |                        | R: tgctctgtagccccggctgcggcata             |
| **TNF gene**                  |                        |                      |                        |                                             |
| rs361525                      | G > A                  | 31543101             | 5'-upstream            | F: ggccagagagaccccctcgggaacctc            |
|                               |                        |                      |                        | R: gaggcagagagatggcagatggag            |
| rs1800629                     | G > A                  | 31543031             | 5'-upstream            | F: gaggcaatagctgctggagccctcag            |
|                               |                        |                      |                        | R: gaggcagagagcttctgaggctcctcc          |
| **CRP gene**                  |                        |                      |                        |                                             |
| rs3093077                     | A > C                  | 159679636            | Not announced          | F: ggaatccagacgaagcagacaaaccc             |
|                               |                        |                      |                        | R: tctgactacagtggcagttgtct              |
| rs1130864                     | G > A                  | 159683091            | 3'-UTR                 | F: cctaatttcatttttttgagacc            |
|                               |                        |                      |                        | R: tttctcctctatcagagatggctctcc        |
| rs1205                        | C > T                  | 159682233            | 3'-UTR                 | F: acctctcagctgctttgtaaaca            |
|                               |                        |                      |                        | R: agttctctctatgcttgccaaacag           |
| **APOB gene**                 |                        |                      |                        |                                             |
| rs1042031                     | C > T                  | 21225753             | Glu4181Lys              | F: caatacagctctgctttcattaggaat            |
|                               |                        |                      |                        | R: ttgatagactgtaccacagcataacaac          |
| rs6725189                     | G > T                  | 21219001             | Not announced          | F: ttccccagctctgctacaacaggtatgggg        |
|                               |                        |                      |                        | R: cagctcgccctctctagtcttttccc          |
| **APOE gene**                 |                        |                      |                        |                                             |
| rs7412                        | C > T                  | 45412079             | Arg176Cys              | F: ctctcccagctgctgtacgctagcaagag          |
|                               |                        |                      |                        | R: gccttcagctgctacagccgggcgcggc         |
rs13290979 polymorphism within the NOTCH1 gene and the G allele of the rs1801197 polymorphism within the CALCR gene were associated with a lower risk of IE (OR = 0.54, 95% CI = 0.34–0.84, p = 0.0062 according to an overdominant model; OR = 0.56, 95% CI = 0.38–0.82, p = 0.0020 according to a log-additive model, resp., Table 4). Other SNPs were not significantly associated with IE (Table 4).

As cytokines are easily detected in blood, we then sought to explore the functional consequences of four SNPs reaching the significance threshold in IL1B, IL12, and CRP genes. We evaluated the plasma levels of these proteins obtained from the patients with IE before admission and 7 days postoperation (Figure 2). The G/A genotype of the rs1143634 polymorphism within the IL1B gene and the G/T genotype of the rs3212227 polymorphism within the IL12B gene were associated with a higher plasma level of IL-1β and IL-12, respectively, at either time point (Figure 2). However, no significant associations were revealed for CRP.

**Table 3: Continued.**

| Single nucleotide polymorphism | Nucleotide substitution | Chromosomal position | Amino acid substitution | Forward 5'–3' and reverse 3'–5' polymerase chain reaction primers |
|--------------------------------|------------------------|----------------------|------------------------|---------------------------------------------------------------|
| rs429358 LIPC gene             | T > C                  | 45411941             | Cys130Arg              | F: gcgcgcgtgggagcgccagaaatagagcgtg R: gcgcgcgtgggatcgcagcggag |
| rs1800588 LPA gene             | C > T                  | 58723675             | 5'-upstream            | F: tttgtcctctctgctccttgccttgacaa R: ggcgatgggtttctgacacactttt |
| rs10455872 NOTCH1 gene         | A > G                  | 161010118            | Intrinsic              | F: tcagacactctgtctcagaaacccca R: tttacccagctacagctacaggag |
| rs13290979 VDR gene            | A > G                  | 139425634            | Intrinsic              | F: cagcagcagctaggaagactgaccccaac R: acctctctgctgacctacggggctt |
| rs2228570 CASR gene            | A > G                  | 48272895             | Met1Thr/Lys/Arg        | F: ggacgagagtggctgcggcattgctcc R: tctctgtaaaacagacagagagggg |
| rs1042636 OPG gene             | A > G                  | 122003769            | Arg990Gly              | F: gatgagccctagaaagcccatgccaccccaac R: gaaattctcagcaccgaaatctcggag |
| rs3134069 CALCR gene           | A > C                  | 119964988            | 5'-upstream            | F: ggacctctacgcgtgaactctggagt R: gcctcgctggttcctacagctcaaa |
| rs2073618 VDR gene             | G > C                  | 119964052            | Asn3Lys                | F: ggacatccacgccgagcgcagacacagaaacaa R: ttgaccttgctgccggcagcggag |
| rs3102735 F2 gene              | T > C                  | 119965070            | 5'-upstream            | F: ctctgctcagttgctgtcctccatcaat R: aatctccggtctagaagttacttgatg |
| rs1801197 F5 gene              | A > G                  | 93055753             | Leu481Pro              | F: tgcctctggttggcctctcctcctcctc R: gcctgtgatgccagctgatggatgatg |
| rs1799963 F7 gene              | G > A                  | 46761055             | 3'-UTR                 | F: gttcacaatataagggcaactcttcac R: agccatgtccacaggtcagtcattc |
| rs6025 ITGB3 gene              | T > C                  | 169519049            | Gln534Arg              | F: taacctcaagacaaataacctgttccct R: gccttgctcaggggatctgcctcaagat |
| rs6027 ITGB3 gene              | T > C                  | 169483561            | Asp2222Gly             | F: gggtttttaagttcagatcctaaata R: cacagccaaagagttcagcagaggtgaa |
| rs6046 ITGB3 gene              | G > A                  | 113773159            | Arg412Gln/Pro/Leu      | F: acaagtggaggccccactggacaccactaccc R: gggccagctgtttgctggagcagcctc |

IL: interleukin; TNF: tumor necrosis factor; CRP: C-reactive protein; APO: apolipoprotein; LIPC: hepatic lipase; LPA: lipoprotein (a); VDR: vitamin D receptor; CASR: calcium-sensing receptor; OPG: osteoprotegerin; CALCR: calcitonin receptor; ITGB: integrin beta.
To further reinforce the associations between the marker SNPs, plasma cytokine levels, and risk of IE, we hypothesized that those SNPs which did not demonstrate a predictive value would not show associations with altered plasma levels of the corresponding proteins. Hence, we performed the similar analysis for the SNPs within the genes encoding cytokines which are generally elevated in patients with IE, that is, TNF-α, IL-6, IL-8, and IL-10 (Supplementary Figures 1 and 2 available online at https://doi.org/10.1155/2017/7962546). Expectedly, no statistically significant associations were found.

4. Discussion

Despite the recent progress in diagnosis and treatment [1, 2], the basis of genetic susceptibility to IE remains vaguely uncovered. Early investigation by Vollmer et al. revealed the G allele of the rs2232596 polymorphism and the T allele of the rs2232582 polymorphism within the LBP gene being associated with a higher risk of IE [29]. As known, lipopolysaccharide-binding protein is released into the bloodstream as an acute phase response protein during IE [19]. Further studies by Daga et al. [30, 31] and Durante-
| Model      | Genotype | Without infective endocarditis | With infective endocarditis | OR (95% CI)       | p value | AIC    | HWE |
|------------|----------|--------------------------------|-----------------------------|-------------------|---------|-------|-----|
|            |          | G/G (51.3%)                    | 154 (67.8%)                 | 1.00              |         |       |     |
| IL1B       | Codominant | G/A (41%)                      | 123 (23.1%)                 | 0.43 (0.26–0.72) | 0.0029  | 472.5 |     |
|            | A/A (7.7%) | 23 (9.1%)                      | 11 (41.9%)                 | 0.97 (0.43–2.18) |         |       |     |
|            | G/G (51.3%) | 154 (67.8%)                   | 82 (67.8%)                 | 1.00              |         |       |     |
| Dominant   | G/A-A/A (48.7%) | 146 (32.2%)         | 39 (72.2%)                 | 0.51 (0.32–0.81) |         |       |     |
|            | G/G-G/G-A/A (92.3%) | 277 (90.9%)         | 110 (90.9%)                | 1.00              |         |       |     |
|            | A/A (7.7%) | 23 (9.1%)                      | 11 (41.9%)                 | 1.30 (0.59–2.88) | 0.52    | 481.8 |     |
| Recessive  | G/G-A/G (59%) | 177 (76.9%)                | 93 (76.9%)                 | 1.00              |         |       |     |
| Overdominant | G/A (41%)                      | 123 (23.1%)         | 28 (23.1%)                 | 0.43 (0.26–0.71) | 0.0016  | 470.6 |     |
| Log-additive | —                          | —                        | 0.70 (0.48–1.00)           | 0.046             | 478.2   |       |     |
| IL6        | rs1554606 | G/G (30.7%)                    | 92 (30.7%)                 | 1.00              |         |       |     |
| Codominant | G/T (49.7%) | 149 (50.8%)                   | 62 (50.8%)                 | 1.38 (0.82–2.33) | 0.31    | 483   |     |
|            | T/T (19.7%) | 59 (23.8%)                     | 29 (23.8%)                 | 1.57 (0.84–2.95) |         |       |     |
|            | G/G (30.7%) | 92 (30.7%)                     | 31 (25.4%)                 | 1.00              |         |       |     |
| Dominant   | G/T-T/T (69.3%) | 208 (74.6%)                | 91 (74.6%)                 | 1.44 (0.87–2.36) | 0.15    | 481.2 |     |
|            | G/G-G/G-T/T (80.3%) | 241 (76.2%)                | 93 (76.2%)                 | 1.00              |         |       |     |
| Recessive  | T/T (19.7%) | 59 (23.8%)                     | 29 (23.8%)                 | 1.28 (0.76–2.17) | 0.36    | 482.5 |     |
| Overdominant | G/G-T/T (50.3%) | 151 (49.2%)                | 60 (49.2%)                 | 1.00              |         |       |     |
| Log-additive | G/T (49.7%)                      | 149 (50.8%)         | 62 (50.8%)                 | 1.13 (0.73–1.76) | 0.58    | 483   |     |
| Log-additive | —                          | —                        | 1.26 (0.92–1.72)           | 0.14               | 481.2   |       |     |
| IL6        | rs1800796 | G/G (86.7%)                    | 260 (86.7%)                | 104 (85.2%)       | 1.00    | 485.3 |     |
| Codominant | C/G (12.7%) | 38 (13.9%)                     | 17 (13.9%)                 | 1.07 (0.56–2.02) | 0.98    | 485.3 |     |
|            | C/C (2%)  | 2 (0.7%)                       | 1 (0.8%)                   | 1.17 (0.08–17.14) |         |       |     |
| Dominant   | G/G (86.7%) | 260 (85.2%)                   | 104 (85.2%)                | 1.00              |         |       |     |
|            | C/G-C/C (13.3%) | 40 (14.8%)                 | 18 (14.8%)                 | 1.07 (0.57–2.00) | 0.83    | 483.3 |     |
|            | G/G-G/G-C/G (99.3%) | 298 (99.2%)                | 121 (99.2%)                | 1.00              |         |       |     |
| Recessive  | C/C (2%)  | 2 (0.7%)                       | 1 (0.8%)                   | 1.16 (0.08–16.99) | 0.91    | 483.3 |     |
| Overdominant | G/G-C/C (87.3%) | 262 (86.1%)                | 105 (86.1%)                | 1.00              |         |       |     |
| Log-additive | G/G (12.7%)                      | 38 (13.9%)         | 17 (13.9%)                 | 1.06 (0.56–2.02) | 0.85    | 483.3 |     |
| Log-additive | —                          | —                        | 1.07 (0.60–1.92)           | 0.82               | 483.3   |       |     |
| Model          | Genotype | Without infective endocarditis | With infective endocarditis | OR (95% CI)  | p value | AIC    | HWE |
|---------------|----------|--------------------------------|-----------------------------|--------------|---------|--------|-----|
| **IL6 rs2069827** |          |                                |                             |              |         |        |     |
| Codominant    | G/G      | G/G (81.7%)                    | 99 (81.2%)                  | 1.00         |         |        |     |
|               | G/T      | G/T (17%)                      | 22 (18%)                    | 1.20 (0.68–2.14) | 0.82   | 484.9  |     |
|               | T/T      | 4 (1.3%)                       | 1 (0.8%)                    | 0.93 (0.10–8.66) | 0.55   |        | 0.51|
| Dominant      | G/G      | G/G (81.7%)                    | 99 (81.2%)                  | 1.00         |         |        |     |
|               | G/T-T/T  | G/T-T/T (18.3%)                | 23 (18.9%)                  | 1.19 (0.68–2.08) | 0.55   | 483    |     |
|               | G/G-G/T  | G/G-G/T (98.7%)                | 121 (99.2%)                 |              |         |        |     |
| Recessive     | T/T      | T/T (1.3%)                     | 1 (0.8%)                    | 0.90 (0.10–8.33) | 0.93   | 483.3  |     |
| Overdominant  | G/G-T/T  | G/G-T/T (83%)                  | 100 (82%)                   | 1.00         |         |        |     |
|               | G/T      | G/T (17%)                      | 22 (18%)                    | 1.20 (0.68–2.14) | 0.53   | 482.9  |     |
|                |          |                                |                             |              |         |        |     |
| **IL6R rs2228145** |        |                                |                             |              |         |        |     |
| Codominant    | A/A      | A/A (48%)                      | 62 (50.8%)                  | 1.00         |         |        |     |
|               | C/A      | C/A (42.3%)                    | 45 (36.9%)                  | 0.84 (0.52–1.34) | 0.46   | 483.8  |     |
|               | C/C      | 29 (9.7%)                      | 15 (12.3%)                  | 1.12 (0.64–2.73) | 0.46   |        |     |
|               | A/A      | 144 (48%)                      | 62 (50.8%)                  | 1.00         |         |        |     |
| Dominant      | C/A-C/C  | C/A-C/C (52%)                  | 60 (49.2%)                  | 0.92 (0.59–1.43) | 0.71   | 483.2  | 0.89|
|               | A/A-C/A  | A/A-C/A (90.3%)                | 107 (87.7%)                 | 1.00         |         |        |     |
| Recessive     | C/C      | C/C (9.7%)                     | 15 (12.3%)                  | 1.43 (0.72–2.87) | 0.32   | 482.3  |     |
| Overdominant  | A/A-C/C  | A/A-C/C (57.7%)                | 77 (63.1%)                  | 1.00         |         |        |     |
|               | C/A      | C/A (42.3%)                    | 45 (36.9%)                  | 0.79 (0.51–1.25) | 0.32   | 482.3  |     |
|                |          |                                |                             |              |         |        |     |
| **IL6R rs2229238** |        |                                |                             |              |         |        |     |
| Codominant    | C/C      | C/C (52.7%)                    | 62 (50.8%)                  | 1.00         |         |        |     |
|               | C/T      | C/T (40.3%)                    | 47 (38.5%)                  | 1.00 (0.63–1.60) | 0.48   | 483.8  |     |
|               | T/T      | 21 (7%)                        | 13 (10.7%)                  | 1.43 (0.73–3.61) | 0.69   | 483.2  | 0.88|
| Dominant      | C/T-T/T  | C/T-T/T (47.3%)                | 60 (49.2%)                  | 1.09 (0.71–1.70) | 0.69   | 483.2  |     |
|               | C/C-C/T  | 279 (93%)                      | 109 (89.3%)                 | 1.00         |         |        |     |
| Recessive     | T/T      | 21 (7%)                        | 13 (10.7%)                  | 1.63 (0.75–3.51) | 0.22   | 481.8  |     |
| Overdominant  | C/C-T/T  | C/C-T/T (59.7%)                | 75 (61.5%)                  | 1.00         |         |        |     |
|               | C/T      | 121 (40.3%)                    | 47 (38.5%)                  | 0.94 (0.60–1.47) | 0.78   | 483.3  |     |
|                |          |                                |                             |              |         |        |     |
| **IL8 rs2227306** |        |                                |                             |              |         |        |     |
| Codominant    | C/C      | C/C (52.7%)                    | 62 (50.8%)                  | 1.00         |         |        |     |
|               | C/T      | C/T (40.3%)                    | 47 (38.5%)                  | 1.00 (0.63–1.60) | 0.48   | 483.8  |     |
|               | T/T      | 21 (7%)                        | 13 (10.7%)                  | 1.63 (0.73–3.61) | 0.69   | 483.2  | 0.88|
| Dominant      | C/T-T/T  | C/T-T/T (47.3%)                | 60 (49.2%)                  | 1.09 (0.71–1.70) | 0.69   | 483.2  |     |
|               | C/C-C/T  | 279 (93%)                      | 109 (89.3%)                 | 1.00         |         |        |     |
| Recessive     | T/T      | 21 (7%)                        | 13 (10.7%)                  | 1.63 (0.75–3.51) | 0.22   | 481.8  |     |
| Overdominant  | C/C-T/T  | C/C-T/T (59.7%)                | 75 (61.5%)                  | 1.00         |         |        |     |
|               | C/T      | 121 (40.3%)                    | 47 (38.5%)                  | 0.94 (0.60–1.47) | 0.78   | 483.3  |     |
|                |          |                                |                             |              |         |        |     |
| **IL8 rs2227306** |        |                                |                             |              |         |        |     |
| Codominant    | C/C      | C/C (52.7%)                    | 62 (50.8%)                  | 1.00         |         |        |     |
|               | C/T      | C/T (40.3%)                    | 47 (38.5%)                  | 1.00 (0.63–1.60) | 0.48   | 483.8  |     |
|               | T/T      | 21 (7%)                        | 13 (10.7%)                  | 1.63 (0.73–3.61) | 0.69   | 483.2  | 0.88|
| Dominant      | C/T-T/T  | C/T-T/T (47.3%)                | 60 (49.2%)                  | 1.09 (0.71–1.70) | 0.69   | 483.2  |     |
|               | C/C-C/T  | 279 (93%)                      | 109 (89.3%)                 | 1.00         |         |        |     |
| Recessive     | T/T      | 21 (7%)                        | 13 (10.7%)                  | 1.63 (0.75–3.51) | 0.22   | 481.8  |     |
| Overdominant  | C/C-T/T  | C/C-T/T (59.7%)                | 75 (61.5%)                  | 1.00         |         |        |     |
|               | C/T      | 121 (40.3%)                    | 47 (38.5%)                  | 0.94 (0.60–1.47) | 0.78   | 483.3  |     |
Table 4: Continued.

| Model       | Genotype | Without infective endocarditis | With infective endocarditis | OR (95% CI)          | p value | AIC     | HWE     |
|-------------|----------|--------------------------------|-----------------------------|----------------------|---------|---------|---------|
| **Codominant** | C/C      | 100 (33.3%)                    | 49 (40.2%)                  | 1.00                 |         |         |         |
|             | C/T      | 147 (49%)                      | 59 (48.4%)                  | 0.83 (0.52–1.33)     | 0.42    | 483.6   |         |
|             | T/T      | 53 (17.7%)                     | 14 (11.5%)                  | 0.63 (0.31–1.28)     |         |         |         |
| **Dominant** | C/T      | 100 (33.3%)                    | 49 (40.2%)                  | 1.00                 |         |         |         |
|             | T/T      | 200 (66.7%)                    | 73 (59.8%)                  | 0.78 (0.50–1.23)     | 0.29    | 482.2   | 0.99    |
| **Recessive** | C/C-C/T | 247 (82.3%)                    | 108 (88.5%)                 | 1.00                 | 0.28    | 482.2   |         |
|             | T/T      | 53 (17.7%)                     | 14 (11.5%)                  | 0.70 (0.37–1.35)     |         |         |         |
| **Overdominant** | C/C-T/T | 153 (51%)                      | 63 (51.6%)                  | 1.00                 | 0.79    | 483.3   |         |
|             | C/T      | 147 (49%)                      | 59 (48.4%)                  | 0.94 (0.61–1.46)     |         |         |         |
| **Log-additive** | —       | —                              | —                           | —                    | 0.19    | 481.6   |         |

*IL10 rs1800871*

| Model       | Genotype | Without infective endocarditis | With infective endocarditis | OR (95% CI)          | p value | AIC     | HWE     |
|-------------|----------|--------------------------------|-----------------------------|----------------------|---------|---------|---------|
| **Codominant** | G/G      | 183 (61%)                      | 69 (56.6%)                  | 1.00                 |         |         |         |
|             | A/G      | 105 (35%)                      | 47 (38.5%)                  | 1.12 (0.71–1.78)     | 0.88    | 485.1   |         |
|             | A/A      | 12 (4%)                        | 6 (4.9%)                    | 0.98 (0.34–2.81)     |         |         |         |
| **Dominant** | G/G      | 183 (61%)                      | 69 (56.6%)                  | 1.00                 |         |         |         |
|             | A/G-A/A  | 117 (39%)                      | 53 (43.4%)                  | 1.11 (0.71–1.73)     | 0.66    | 483.1   | 0.61    |
| **Recessive** | G/G-A/G | 288 (96%)                      | 116 (95.1%)                 | 1.00                 | 0.9     | 483.3   |         |
|             | A/A      | 12 (4%)                        | 6 (4.9%)                    | 0.94 (0.33–2.64)     |         |         |         |
| **Overdominant** | G/G-A/A | 195 (65%)                      | 75 (61.5%)                  | 1.00                 | 0.61    | 483.1   |         |
|             | A/G      | 105 (35%)                      | 47 (38.5%)                  | 1.13 (0.71–1.77)     |         |         |         |
| **Log-additive** | —       | —                              | —                           | —                    | 0.74    | 483.2   |         |

*IL10 rs1800872*

| Model       | Genotype | Without infective endocarditis | With infective endocarditis | OR (95% CI)          | p value | AIC     | HWE     |
|-------------|----------|--------------------------------|-----------------------------|----------------------|---------|---------|---------|
| **Codominant** | G/G      | 185 (62.1%)                    | 67 (55.4%)                  | 1.00                 |         |         |         |
|             | T/G      | 101 (33.9%)                    | 49 (40.5%)                  | 1.27 (0.80–2.01)     | 0.55    | 481.3   |         |
|             | T/T      | 12 (4%)                        | 5 (4.1%)                    | 0.86 (0.28–2.61)     |         |         |         |
| **Dominant** | G/G      | 185 (62.1%)                    | 67 (55.4%)                  | 1.00                 |         |         |         |
|             | T/G-T/T  | 113 (37.9%)                    | 54 (44.6%)                  | 1.22 (0.78–1.90)     | 0.39    | 479.8   | 0.86    |
| **Recessive** | G/G-T/G | 286 (96%)                      | 116 (95.9%)                 | 1.00                 | 0.65    | 480.3   |         |
|             | T/T      | 12 (4%)                        | 5 (4.1%)                    | 0.78 (0.26–2.34)     |         |         |         |
| **Overdominant** | G/G-T/G | 197 (66.1%)                    | 72 (59.5%)                  | 1.00                 | 0.29    | 479.4   |         |
|             | T/G      | 101 (33.9%)                    | 49 (40.5%)                  | 1.28 (0.81–2.01)     |         |         |         |
| **Log-additive** | —       | —                              | —                           | —                    | 0.57    | 480.2   |         |
| Model           | Genotype | Without infective endocarditis | With infective endocarditis | OR (95% CI) | p value | AIC   | HWE |
|-----------------|----------|--------------------------------|-----------------------------|-------------|---------|-------|-----|
|                |          | T/T                            | 88 (29.3%)                  | 34 (28.1%)  | 1.00    |       |     |
| Codominal       |          | T/C                            | 157 (52.3%)                 | 66 (54.5%)  | 1.17 (0.70–1.95) | 0.82 | 481.7 |
|                 |          | C/C                            | 55 (18.3%)                  | 21 (17.4%)  | 1.17 (0.59–2.29) |       |     |
| Dominant        |          | T/T                            | 88 (29.3%)                  | 34 (28.1%)  | 1.00    |       |     |
|                 |          | T/C-C/C                        | 212 (70.7%)                 | 87 (71.9%)  | 1.17 (0.71–1.91) |       |     |
| Recessive       |          | C/C                            | 55 (18.3%)                  | 21 (17.4%)  | 1.05 (0.59–1.88) | 0.87 | 480   |
|                 |          | T/T-T/C                        | 245 (81.7%)                 | 100 (82.6%) | 1.00    |       |     |
| Overdominant    |          | T/C                            | 157 (52.3%)                 | 66 (54.5%)  | 1.10 (0.71–1.72) | 0.66 | 479.9 |
| Log-additive    |          | —                              | —                           | —           | 1.09 (0.78–1.52) | 0.61 | 479.8 |
|                |          | T/T                            | 191 (63.7%)                 | 86 (70.5%)  | 1.00    |       |     |
| IL12B rs3212227 |          | G/T                            | 96 (32%)                    | 29 (23.8%)  | 0.57 (0.34–0.96) | 0.076| 480.2 |
|                 |          | G/G                            | 13 (4.3%)                   | 7 (5.7%)    | 1.20 (0.45–3.24) |       |     |
|                 |          | T/T                            | 191 (63.7%)                 | 86 (70.5%)  | 1.00    |       |     |
| Dominant        |          | G/T-G/G                        | 109 (36.3%)                 | 36 (29.5%)  | 0.64 (0.40–1.04) | 0.067| 480   |
|                 |          | T/T-G/T                        | 287 (95.7%)                 | 115 (94.3%) | 1.00    |       |     |
| Recessive       |          | G/G                            | 13 (4.3%)                   | 7 (5.7%)    | 1.41 (0.53–3.75) | 0.5  | 482.9 |
|                 |          | T/T-G/G                        | 204 (68%)                   | 93 (76.2%)  | 1.00    |       |     |
| Overdominant    |          | G/T                            | 96 (32%)                    | 29 (23.8%)  | 0.57 (0.34–0.94) | 0.025| 478.3 |
| Log-additive    |          | —                              | —                           | —           | 0.78 (0.53–1.16) | 0.21 | 481.8 |
|                |          | A/A                            | 137 (45.7%)                 | 53 (43.4%)  | 1.00    |       |     |
| IL12RB rs375947 |          | A/G                            | 135 (45%)                   | 55 (45.1%)  | 1.18 (0.74–1.89) | 0.58 | 484.3 |
|                 |          | G/G                            | 28 (9.3%)                   | 14 (11.5%)  | 1.44 (0.68–3.03) |       |     |
|                 |          | A/A                            | 137 (45.7%)                 | 53 (43.4%)  | 1.00    |       |     |
| Dominant        |          | A/G-G/G                        | 163 (54.3%)                 | 69 (56.6%)  | 1.23 (0.79–1.91) | 0.37 | 482.5 |
|                 |          | A/A-A/G                        | 272 (90.7%)                 | 108 (88.5%) | 1.00    |       |     |
| Recessive       |          | G/G                            | 28 (9.3%)                   | 14 (11.5%)  | 1.32 (0.65–2.68) | 0.45 | 482.7 |
|                 |          | A/A-G/G                        | 165 (55%)                   | 67 (54.9%)  | 1.00    |       |     |
| Overdominant    |          | A/G                            | 135 (45%)                   | 55 (45.1%)  | 1.10 (0.71–1.72) | 0.66 | 483.1 |
| Log-additive    |          | —                              | —                           | —           | 1.19 (0.85–1.67) | 0.3  | 482.3 |
| Model         | Genotype | Without infective endocarditis | With infective endocarditis | OR (95% CI)     | p value | AIC    | HWE |
|--------------|----------|-------------------------------|-----------------------------|-----------------|---------|-------|-----|
| **TNF rs361525** |          |                               |                             |                 |         |       |     |
| Codominant   | G/G      | 274 (91.3%)                   | 112 (91.8%)                 | 1.00            | 0.81    | 484.9 |     |
|              | A/G      | 25 (8.3%)                     | 10 (8.2%)                   | 0.90 (0.40–1.99)| 0.74    | 483.2 | 0.46|
|              | A/A      | 1 (0.3%)                      | 0 (0%)                      | 0.00 (0.00–NA)  |         |       |     |
| Dominant     | G/G      | 274 (91.3%)                   | 112 (91.8%)                 | 1.00            | 0.55    | 483   |     |
|              | A/G-A/A  | 26 (8.7%)                     | 10 (8.2%)                   | 0.88 (0.39–1.94)|         |       |     |
|              | A/A      | 1 (0.3%)                      | 0 (0%)                      | 0.00 (0.00–NA)  |         |       |     |
| Recessive    | G/G-G/A/G| 299 (99.7%)                   | 122 (100%)                  | 1.00            |         |       |     |
|              | A/A      | 1 (0.3%)                      | 0 (0%)                      | 0.00 (0.00–NA)  |         |       |     |
| Overdominant | G/G-A/A  | 275 (91.7%)                   | 112 (91.8%)                 | 1.00            | 0.79    | 483.3 |     |
|              | A/G      | 25 (8.3%)                     | 10 (8.2%)                   | 0.90 (0.40–2.00)| 0.7     | 483.2 |     |
| Log-additive |          |                               |                             |                 | 0.86    | 483.2 |     |
| **TNF rs1800629** |        |                               |                             |                 |         |       |     |
| Codominant   | G/G      | 229 (76.3%)                   | 97 (79.5%)                  | 1.00            |         |       |     |
|              | A/G      | 67 (22.3%)                    | 24 (19.7%)                  | 0.89 (0.51–1.54)| 0.66    | 484.5 |     |
|              | A/A      | 4 (1.3%)                      | 1 (0.8%)                    | 0.41 (0.04–3.93)|         |       |     |
| Dominant     | G/G      | 229 (76.3%)                   | 97 (79.5%)                  | 1.00            |         |       | 0.99|
|              | A/G-A/A  | 71 (23.7%)                    | 25 (20.5%)                  | 0.85 (0.50–1.46)| 0.56    | 483   |     |
|              | A/A      | 4 (1.3%)                      | 1 (0.8%)                    | 0.42 (0.04–4.02)|         |       |     |
| Recessive    | G/G-G/A/G| 296 (98.7%)                   | 121 (99.2%)                 | 1.00            |         |       |     |
|              | A/A      | 4 (1.3%)                      | 1 (0.8%)                    | 0.42 (0.04–4.02)|         |       |     |
| Overdominant | G/G-A/A  | 233 (77.7%)                   | 98 (80.3%)                  | 1.00            |         |       |     |
|              | A/G      | 67 (22.3%)                    | 24 (19.7%)                  | 0.90 (0.52–1.55)| 0.71    | 483.2 |     |
| Log-additive |          |                               |                             |                 | 0.83    | 483.2 |     |
| **CRP rs3093077** |       |                               |                             |                 |         |       |     |
| Codominant   | C/C      | 262 (87.3%)                   | 112 (92.6%)                 | 1.00            |         |       |     |
|              | A/C      | 37 (12.3%)                    | 8 (6.6%)                    | 0.55 (0.24–1.23)| 0.28    | 481.4 |     |
|              | A/A      | 1 (0.3%)                      | 1 (0.8%)                    | 1.99 (0.12–34.12)|         |       |     |
| Dominant     | C/C      | 262 (87.3%)                   | 112 (92.6%)                 | 1.00            |         |       | 0.99|
|              | A/C-A/A  | 38 (12.7%)                    | 9 (7.4%)                    | 0.59 (0.27–1.29)| 0.17    | 480.2 |     |
|              | A/A      | 1 (0.3%)                      | 1 (0.8%)                    | 2.10 (0.12–36.04)|         |       |     |
| Recessive    | C/C-C/A/C| 299 (99.7%)                   | 120 (99.2%)                 | 1.00            |         |       |     |
|              | A/A      | 1 (0.3%)                      | 1 (0.8%)                    | 2.10 (0.12–36.04)|         |       |     |
| Overdominant | C/C-A/A  | 263 (87.7%)                   | 113 (93.4%)                 | 1.00            |         |       |     |
|              | A/C      | 37 (12.3%)                    | 8 (6.6%)                    | 0.55 (0.24–1.23)| 0.13    | 479.7 |     |
| Log-additive |          |                               |                             |                 | 0.67    | 480.7 |     |
| Model      | Genotype | Without infective endocarditis | With infective endocarditis | OR (95% CI) | p value | AIC  | HWE |
|------------|----------|---------------------------------|-------------------------------|-------------|---------|------|-----|
| **CRP rs1130864** |          |                                 |                               |             |         |      |     |
| Codominant | G/G      | 142 (47.3%)                     | 68 (55.7%)                    | 1.00        |         |      |     |
|            | A/G      | 134 (44.7%)                     | 38 (31.1%)                    | 0.58 (0.36–0.93) | 0.018   | 477.9 |     |
|            | A/A      | 24 (8%)                         | 16 (13.1%)                    | 1.45 (0.70–3.00) |         |      |     |
| Dominant   | G/G      | 142 (47.3%)                     | 68 (55.7%)                    | 1.00        |         |      |     |
|            | A/G-A/A  | 158 (52.7%)                     | 54 (44.3%)                    | 0.71 (0.45–1.09) | 0.12    | 481.4 | 0.41|
| Recessive  | G/G      | 276 (92%)                       | 106 (86.9%)                   | 1.00        | 0.12    | 481.1 |     |
|            | A/A      | 24 (8%)                         | 16 (13.1%)                    | 1.83 (0.91–3.69) |         |      |     |
| Overdominant | A/G    | 166 (55.3%)                     | 84 (68.8%)                    | 1.00        | 0.094   | 476.9 |     |
|            |          |                                 |                               | 1.45 (0.70–3.00) |         |      |     |
| Log-additive | —       |                                  |                               |             |         |      |     |

| **CRP rs1205** |          |                                 |                               |             |         |      |     |
| Codominant | C/C      | 112 (37.3%)                     | 38 (31.9%)                    | 1.00        |         |      |     |
|            | C/T      | 154 (51.3%)                     | 56 (47.1%)                    | 1.06 (0.64–1.74) | 0.018   | 468.4 |     |
|            | T/T      | 34 (11.3%)                      | 25 (21%)                      | 2.50 (1.28–4.90) |         |      |     |
| Dominant   | C/C      | 112 (37.3%)                     | 38 (31.9%)                    | 1.00        |         |      |     |
|            | C/T-T/T  | 188 (62.7%)                     | 81 (68.1%)                    | 1.29 (0.81–2.07) | 0.28    | 473.3 | 0.11|
| Recessive  | C/C      | 266 (88.7%)                     | 94 (79%)                      | 1.00        | 0.0047  | 466.5 |     |
|            | T/T      | 34 (11.3%)                      | 25 (21%)                      | 2.42 (1.32–4.43) |         |      |     |
| Overdominant | C/C    | 146 (48.7%)                     | 63 (52.9%)                    | 1.00        |         |      |     |
|            | C/T      | 154 (51.3%)                     | 56 (47.1%)                    | 0.80 (0.52–1.25) | 0.34    | 473.6 |     |
| Log-additive | —       |                                  |                               |             |         |      |     |

| **APOB rs1042031** |          |                                 |                               |             |         |      |     |
| Codominant | C/C      | 210 (70.5%)                     | 83 (69.8%)                    | 1.00        |         |      |     |
|            | C/T      | 78 (26.2%)                      | 33 (27.7%)                    | 1.00 (0.61–1.65) | 0.86    | 477.7 |     |
|            | T/T      | 10 (3.4%)                       | 3 (2.5%)                      | 0.69 (0.18–2.71) |         |      |     |
| Dominant   | C/C      | 210 (70.5%)                     | 83 (69.8%)                    | 1.00        |         |      |     |
|            | C/T-T/T  | 88 (29.5%)                      | 36 (30.2%)                    | 0.96 (0.59–1.56) | 0.88    | 476  | 0.40|
| Recessive  | C/C      | 288 (96.6%)                     | 116 (97.5%)                   | 1.00        | 0.59    | 475.7 |     |
|            | T/T      | 10 (3.4%)                       | 3 (2.5%)                      | 0.69 (0.18–2.69) |         |      |     |
| Overdominant | C/C    | 220 (73.8%)                     | 86 (72.3%)                    | 1.00        |         |      |     |
|            | C/T      | 78 (26.2%)                      | 33 (27.7%)                    | 1.01 (0.62–1.67) | 0.95    | 476  |     |
| Log-additive | —       |                                  |                               |             |         |      |     |

Mediators of Inflammation
| Model       | Genotype       | Without infective endocarditis | With infective endocarditis | OR (95% CI)     | p value | AIC   | HWE |
|------------|----------------|-------------------------------|----------------------------|-----------------|---------|-------|-----|
| **APOB rs6725189** |               |                               |                            |                 |         |       |     |
| Codominant | G/G            | 196 (65.8%)                   | 72 (59.5%)                 | 1.00            | 0.53    | 481.2 |     |
|            | G/T            | 89 (29.9%)                    | 44 (36.4%)                 | 1.31 (0.82–2.10)| 0.3     | 479.4 | 0.46|
|            | T/T            | 13 (4.4%)                     | 5 (4.1%)                   | 1.01 (0.33–3.04)| 0.3     | 479.4 |     |
| Dominant   | G/G            | 196 (65.8%)                   | 72 (59.5%)                 | 1.00            | 0.3     | 480.5 |     |
|            | G/T-G/T/T      | 102 (34.2%)                   | 49 (40.5%)                 | 1.27 (0.81–2.00)| 0.3     | 479.2 |     |
| Recessive  | T/T            | 13 (4.4%)                     | 5 (4.1%)                   | 0.92 (0.31–2.73)| 0.26    | 479.2 |     |
| Overdominant | G/G-G/T/T    | 285 (95.6%)                   | 116 (95.9%)                | 1.00            | 0.26    | 479.2 |     |
|            | G/T            | 89 (29.9%)                    | 44 (36.4%)                 | 1.31 (0.82–2.08)| 0.26    | 479.2 |     |
| Log-additive | —              | —                             | —                          | 1.17 (0.80–1.71)| 0.42    | 479.9 |     |
| **APOE rs7412** |               |                               |                            |                 |         |       |     |
| Codominant | C/C            | 251 (83.7%)                   | 104 (86%)                  | 1.00            | 0.63    | 483.2 |     |
|            | C/T            | 48 (16%)                      | 16 (13.2%)                 | 0.79 (0.42–1.49)| 0.3     | 481.7 | 0.71|
|            | T/T            | 1 (0.3%)                      | 1 (0.8%)                   | 2.37 (0.13–4.65)| 0.53    | 481.7 |     |
| Dominant   | C/T-G/T/T      | 251 (83.7%)                   | 104 (86%)                  | 1.00            | 0.53    | 481.7 |     |
|            | C/C-C/T/T      | 299 (99.7%)                   | 120 (99.2%)                | 1.00            | 0.55    | 481.7 |     |
| Recessive  | T/T            | 1 (0.3%)                      | 1 (0.8%)                   | 2.45 (0.13–45.09)| 0.44    | 481.5 |     |
| Overdominant | C/C-T/T/T     | 252 (84%)                     | 105 (86.8%)                | 1.00            | 0.44    | 481.5 |     |
|            | C/T            | 48 (16%)                      | 16 (13.2%)                 | 0.78 (0.42–1.48)| 0.44    | 481.5 |     |
| Log-additive | —              | —                             | —                          | 0.86 (0.48–1.56)| 0.63    | 481.8 |     |
| **APOE rs429358** |               |                               |                            |                 |         |       |     |
| Codominant | T/T            | 239 (79.7%)                   | 96 (78.7%)                 | 1.00            | 0.71    | 485.2 |     |
|            | C/C            | 58 (19.3%)                    | 24 (19.7%)                 | 1.22 (0.70–2.14)| 0.44    | 483.3 | 0.99|
|            | C/T            | 3 (1%)                        | 2 (1.6%)                   | 1.58 (0.24–10.40)| 0.44    | 483.7 |     |
| Dominant   | C/T-C/C        | 239 (79.7%)                   | 96 (78.7%)                 | 1.00            | 0.44    | 483.3 |     |
|            | T/T-C/T/T      | 297 (99%)                     | 120 (98.4%)                | 1.00            | 0.67    | 483.7 |     |
| Recessive  | T/T-C/T        | 242 (80.7%)                   | 98 (80.3%)                 | 1.00            | 0.5     | 483.4 |     |
| Overdominant | C/T-C/T/C      | 58 (19.3%)                    | 24 (19.7%)                 | 1.21 (0.69–2.12)| 0.41    | 483.2 |     |
| Log-additive | —              | —                             | —                          | 1.23 (0.75–2.01)|         |       |     |
| Model          | Genotype     | Without infective endocarditis | With infective endocarditis | OR (95% CI) | p value | AIC     | HWE   |
|---------------|--------------|---------------------------------|----------------------------|-------------|---------|---------|-------|
| LIPC rs1800588| Codominant   |                                 |                            |             |         |         |       |
|               | C/C          | 173 (57.7%)                     | 77 (63.6%)                 | 1.00        | 0.2     | 480.8   | 0.52  |
|               | C/T          | 113 (37.7%)                     | 41 (33.9%)                 | 0.69 (0.43–1.11) | 0.084   | 479.1   |       |
|               | T/T          | 14 (4.7%)                       | 3 (2.5%)                   | 0.48 (0.13–1.81) |         |         |       |
|               | Dominant     |                                 |                            |             |         |         |       |
|               | C/C          | 173 (57.7%)                     | 77 (63.6%)                 | 1.00        | 0.084   | 479.1   |       |
|               | C/T-T/T      | 127 (42.3%)                     | 44 (36.4%)                 | 0.67 (0.43–1.06) |        |         |       |
|               | C/C-T/T      | 286 (95.3%)                     | 118 (97.5%)                | 1.00        | 0.35    | 481.2   |       |
|               | Recessive    |                                 |                            |             |         |         |       |
|               | T/T          | 14 (4.7%)                       | 3 (2.5%)                   | 0.55 (0.15–2.03) | 0.16    | 480.1   |       |
|               | Overdominant |                                 |                            |             |         |         |       |
|               | C/T          | 113 (37.7%)                     | 41 (33.9%)                 | 0.72 (0.45–1.15) |        |         |       |
|               | Log-additive |                                 |                            |             |         |         |       |
|               | A/A          | 275 (92%)                       | 108 (91.5%)                | 1.00        | 0.86    | 475.8   | 0.99  |
|               | A/G          | 24 (8%)                         | 10 (8.5%)                  | 1.08 (0.48–2.39) |        |         |       |
| NOTCH1 rs13290979 | Codominant |                                 |                            |             |         |         |       |
|               | A/A          | 98 (32.8%)                      | 53 (43.8%)                 | 1.00        | 0.024   | 476.2   |       |
|               | A/G          | 152 (50.8%)                     | 44 (36.4%)                 | 0.53 (0.33–0.87) |        |         |       |
|               | G/G          | 49 (16.4%)                      | 24 (19.8%)                 | 0.98 (0.53–1.82) |        |         |       |
|               | Dominant     |                                 |                            |             |         |         |       |
|               | A/G-G/G      | 201 (67.2%)                     | 68 (56.2%)                 | 0.64 (0.41–1.00) | 0.05    | 477.9   | 0.48  |
|               | A/A-A/G      | 250 (83.6%)                     | 97 (80.2%)                 | 1.00        | 0.28    | 480.6   |       |
|               | Recessive    |                                 |                            |             |         |         |       |
|               | G/G          | 49 (16.4%)                      | 24 (19.8%)                 | 1.37 (0.78–2.41) |        |         |       |
|               | Overdominant |                                 |                            |             |         |         |       |
|               | A/G          | 152 (50.8%)                     | 44 (36.4%)                 | 0.54 (0.34–0.84) | 0.0062  | 474.2   |       |
|               | Log-additive |                                 |                            |             |         |         |       |
|               | VDR rs2228570 |                                 |                            |             |         |         |       |
|               | G/G          | 94 (31.5%)                      | 36 (29.8%)                 | 1.00        | 0.19    | 479.1   |       |
|               | Codominant   |                                 |                            |             |         |         |       |
|               | A/G          | 145 (48.7%)                     | 51 (42.1%)                 | 0.93 (0.55–1.57) |        |         |       |
|               | A/A          | 59 (19.8%)                      | 34 (28.1%)                 | 1.54 (0.85–2.80) |        |         |       |
|               | G/G          | 94 (31.5%)                      | 36 (29.8%)                 | 1.00        | 0.67    | 480.3   | 0.81  |
|               | Dominant     |                                 |                            |             |         |         |       |
|               | A/G-A/A      | 204 (68.5%)                     | 85 (70.2%)                 | 1.11 (0.69–1.79) |        |         |       |
|               | G/G-A/G      | 239 (80.2%)                     | 87 (71.9%)                 | 1.00        | 0.07    | 477.2   |       |
|               | Recessive    |                                 |                            |             |         |         |       |
|               | A/A          | 59 (19.8%)                      | 34 (28.1%)                 | 1.61 (0.97–2.68) |        |         |       |
|               | Overdominant |                                 |                            |             |         |         |       |
|               | G/G-A/A      | 153 (51.3%)                     | 70 (57.9%)                 | 1.00        | 0.25    | 479.2   |       |
| Model                  | Genotype | Without infective endocarditis | With infective endocarditis | OR (95% CI)     | p value | AIC  | HWE  |
|------------------------|----------|--------------------------------|-----------------------------|-----------------|---------|------|------|
| **Log-additive**        | **A/G**  | 145 (48.7%)                    | 51 (42.1%)                  | 0.77 (0.50–1.20)| 0.19    | 478.8|
| **CASR rs1042636**     | **A/A**  | 244 (81.6%)                    | 103 (85.1%)                 | 1.23 (0.91–1.66)| 0.19    | 480  |
| **Codominant**         | **A/G**  | 52 (17.4%)                     | 18 (14.9%)                  | 0.71 (0.39–1.30)| 0.2     | 480  |
| **G/G**                | **A/A**  | 244 (81.6%)                    | 103 (85.1%)                 | 0.00 (0.00–NA)  | 0.19    | 479.8|
| **Dominant**           | **A/G-G/G** | 55 (18.4%)                  | 18 (14.9%)                  | 0.67 (0.37–1.23)| 0.19    | 480  |
| **Recessive**          | **A/A-A/G** | 296 (99%)                  | 121 (100%)                  | 1.00             | 0.16    | 479.8|
| **Overdominant**       | **A/A-G/G** | 247 (82.6%)                  | 103 (85.1%)                 | 1.00             | 0.28    | 480  |
| **Log-additive**       | **A/G**  | 52 (17.4%)                     | 18 (14.9%)                  | 0.72 (0.39–1.32)| 0.14    | 479.6|
| **OPG rs3134069**      | **A/A**  | 248 (83.2%)                    | 110 (90.9%)                 | 1.00             | 0.19    | 479.2|
| **Codominant**         | **A/C**  | 49 (16.4%)                     | 10 (8.3%)                   | 0.53 (0.25–1.11)| 0.86    | 479.9|
| **C/C**                | **A/C**  | 1 (0.3%)                       | 1 (0.8%)                    | 1.92 (0.09–41.36)| 0.71    | 480  |
| **Dominant**           | **A/C-C/C** | 50 (16.8%)                  | 11 (9.1%)                   | 0.56 (0.28–1.15)| 0.71    | 480  |
| **Recessive**          | **A/A-A/C** | 297 (99.7%)                  | 120 (99.2%)                 | 1.00             | 0.078   | 477.4|
| **Overdominant**       | **A/A-C/C** | 249 (83.6%)                  | 111 (91.7%)                 | 1.00             | 0.078   | 477  |
| **Log-additive**       | **A/C**  | 49 (16.4%)                     | 10 (8.3%)                   | 0.53 (0.25–1.11)| 0.15    | 479.4|
| **OPG rs2073618**      | **C/C**  | 76 (25.4%)                     | 32 (26.7%)                  | 1.00             | 0.15    | 479.4|
| **Codominant**         | **C/G**  | 155 (51.8%)                    | 51 (42.5%)                  | 0.79 (0.46–1.36)| 0.17    | 478.3|
| **G/G**                | **C/C**  | 68 (22.7%)                     | 37 (30.8%)                  | 1.32 (0.73–2.41)| 0.86    | 479.9|
| **Dominant**           | **C/G-G/G** | 223 (74.6%)                  | 88 (73.3%)                  | 0.96 (0.58–1.58)| 0.56    | 477  |
| **Recessive**          | **C/C-C/G** | 231 (77.3%)                  | 83 (69.2%)                  | 1.00             | 0.089   | 477  |
| **Overdominant**       | **C/G**  | 68 (22.7%)                     | 37 (30.8%)                  | 1.54 (0.94–2.52)| 0.098   | 477.2|
Table 4: Continued.

| Model       | Genotype  | Without infective endocarditis | With infective endocarditis | OR (95% CI)   | p value | AIC     | HWE     |
|-------------|-----------|---------------------------------|-----------------------------|--------------|--------|--------|--------|
| Log-additive| —         | —                               | —                           | 1.16 (0.85–1.58) | 0.35   | 479    |        |
| OPG rs3102735 | T/T       | 218 (73.2%)                     | 95 (78.5%)                  | 1.00         |        |        |        |
| Codominant  | C/T       | 73 (24.5%)                      | 25 (20.7%)                  | 0.89 (0.52–1.52) | 0.36   | 480.4  |        |
|            | C/C       | 7 (2.4%)                        | 1 (0.8%)                    | 0.25 (0.03–2.27) |        |        |        |
| Dominant    | T/T       | 218 (73.2%)                     | 95 (78.5%)                  | 1.00         | 0.46   | 480    | 0.82   |
| Recessive   | C/T-C/C   | 80 (26.9%)                      | 26 (21.5%)                  | 0.82 (0.49–1.39) | 0.17   | 478.6  |        |
| Overdominant| T/T-C/T   | 291 (97.7%)                     | 120 (99.2%)                 | 1.00         | 0.74   | 480.4  |        |
| Log-additive| —         | —                               | —                           | 0.78 (0.49–1.26) | 0.3    | 479.4  |        |
| CALCR rs1801197 | A/A       | 140 (46.8%)                     | 76 (62.8%)                  | 1.00         |        |        |        |
| Codominant  | A/G       | 136 (45.5%)                     | 40 (33.1%)                  | 0.52 (0.33–0.84) | 0.0077 | 474    |        |
|            | G/G       | 23 (7.7%)                       | 5 (4.1%)                    | 0.36 (0.13–1.03) |        |        |        |
| Dominant    | A/A       | 140 (46.8%)                     | 76 (62.8%)                  | 1.00         |        |        |        |
| Recessive   | A/G-A/G   | 159 (53.2%)                     | 45 (37.2%)                  | 0.50 (0.32–0.79) | 0.0024 | 472.5  | 0.22   |
| Overdominant| A/A-G/G   | 276 (92.3%)                     | 116 (95.9%)                 | 1.00         | 0.13   | 479.5  |        |
| Log-additive| —         | —                               | —                           | 0.56 (0.38–0.82) | 0.002  | 472.2  |        |
| F2 rs1799963 | G/G       | 286 (95.7%)                     | 118 (98.3%)                 | 1.00         | 0.10   | 477    | 0.99   |
|            | A/G       | 13 (4.3%)                       | 2 (1.7%)                    | 0.32 (0.07–1.49) |        |        |        |
| F5 rs6025   | C/C       | 286 (95.7%)                     | 117 (97.5%)                 | 1.00         |        |        |        |
| Codominant  | C/T       | 12 (4%)                         | 3 (2.5%)                    | 0.56 (0.15–2.11) | 0.32   | 479.4  | 0.14   |
| Dominant    | C/C       | 286 (95.7%)                     | 117 (97.5%)                 | 1.00         | 0.24   | 478.3  |        |
| Model        | Genotype | Without infective endocarditis | With infective endocarditis | OR (95% CI)  | p value | AIC    | HWE  |
|-------------|----------|-------------------------------|----------------------------|--------------|---------|-------|------|
|             |          | 13 (4.3%)                     | 3 (2.5%)                   | 0.48 (0.13–1.79) |         |       |      |
| Recessive   | C/T-T/T  | 298 (99.7%)                   | 120 (100%)                 | 1.00         | 0.23    | 478.2 |
|             | C/C-C/T  | 0 (0%)                        | 0.00 (0.00–NA)             |              |         |       |      |
| Overdominant| C/C-T/T  | 12 (4%)                       | 3 (2.5%)                   | 0.57 (0.15–2.13) |         |       |      |
| Log-additive| —        | —                             | —                          | 0.47 (0.14–1.58) |         |       |      |
|ITG5 rs6027  | T/T      | 254 (85%)                     | 104 (86.7%)                | 1.00         | 0.35    | 479.5 |
|             | C/T      | 41 (13.7%)                    | 16 (13.3%)                 | 1.00 (0.52–1.91) | 0.79    | 479.6 |
|             | C/C      | 4 (1.3%)                      | 0 (0%)                     | 0.00 (0.00–NA) |         |       |      |
| Dominant    | T/T      | 254 (85%)                     | 104 (86.7%)                | 1.00         | 0.98    | 479.6 |
|             | C/T-C/C  | 45 (15.1%)                    | 16 (13.3%)                 | 0.92 (0.48–1.74) |         |       |      |
|             | T/T-C/T  | 295 (98.7%)                   | 120 (100%)                 | 1.00         | 0.15    | 479.5 |
|             | C/C      | 4 (1.3%)                      | 0 (0%)                     | 0.00 (0.00–NA) |         |       |      |
| Codominant  | G/G      | 236 (78.9%)                   | 88 (72.7%)                 | 1.00         | 0.06    | 477.8 |
|             | A/G      | 59 (19.7%)                    | 33 (27.3%)                 | 1.58 (0.94–2.64) |         |       |      |
|             | A/A      | 4 (1.3%)                      | 0 (0%)                     | 0.00 (0.00–NA) |         |       |      |
| Recessive   | G/G      | 236 (78.9%)                   | 88 (72.7%)                 | 1.00         | 0.14    | 479.2 |
|             | A/G-A/A  | 63 (21.1%)                    | 33 (27.3%)                 | 1.48 (0.89–2.46) |         |       |      |
| Dominant    | G/G-A/G  | 295 (98.7%)                   | 121 (100%)                 | 1.00         | 0.1     | 478.8 |
|             | A/A      | 4 (1.3%)                      | 0 (0%)                     | 0.00 (0.00–NA) |         |       |      |
| Overdominant| G/G-A/A  | 240 (80.3%)                   | 88 (72.7%)                 | 1.00         | 0.074   | 478.2 |
| Log-additive| A/G      | 59 (19.7%)                    | 33 (27.3%)                 | 1.60 (0.96–2.68) |         |       |      |
|ITGB3 rs5918 | T/T      | 214 (71.6%)                   | 88 (73.3%)                 | 1.00         | 0.5     | 480.2 |
| Codominant  | T/T      | 214 (71.6%)                   | 88 (73.3%)                 | 1.00         | 0.66    |       |      |
| Model           | Genotype | Without infective endocarditis | With infective endocarditis | OR (95% CI)   | p value | AIC  | HWE |
|----------------|----------|---------------------------------|----------------------------|---------------|---------|------|-----|
|                | C/T      | 77 (25.8%)                      | 26 (21.7%)                 | 0.84 (0.49–1.43) |         |      |     |
|                | C/C      | 8 (2.7%)                        | 6 (5%)                     | 1.69 (0.55–5.19) |         |      |     |
| Dominant       | T/T      | 214 (71.6%)                     | 88 (73.3%)                 | 1.00          | 0.76    | 479.5|
|                | C/T-C/C  | 85 (28.4%)                      | 32 (26.7%)                 | 0.93 (0.56–1.52) |         |      |     |
|                | T/T-C/T  | 291 (97.3%)                     | 114 (95%)                  | 1.00          | 0.32    | 478.6|
| Recessive      | C/C      | 8 (2.7%)                        | 6 (5%)                     | 1.77 (0.58–5.39) |         |      |     |
|                | T/T-C/C  | 222 (74.2%)                     | 94 (78.3%)                 | 1.00          | 0.45    | 479  |
| Overdominant   | C/T      | 77 (25.8%)                      | 26 (21.7%)                 | 0.82 (0.48–1.38) |         |      |     |
| Log-additive   | —        | —                               | —                          | 1.02 (0.68–1.54) | 0.92    | 479.6|

All the ORs and 95% CIs are adjusted for age and gender. IL: interleukin; TNF: tumor necrosis factor; CRP: C-reactive protein; APO: apolipoprotein; LIPC: hepatic lipase; LPA: lipoprotein (a); VDR: vitamin D receptor; CASR: calcium-sensing receptor; OPG: osteoprotegerin; CALCR: calcitonin receptor; ITGB: integrin beta; OR: odds ratio; CI: confidence interval; AIC: Akaike information criterion; HWE: Hardy-Weinberg equilibrium.
Mangoni et al. [32] did not find any association between the SNPs within the hemostasis genes (PTH, FV, GPIb, GPIIIa, and FcyRIla) and IE. Our previous study identified the C/C genotype of the rs3775073 polymorphism within the TLR6 gene as a protective factor [12] while a study by Bustamante et al. suggested the A allele of the rs5743708 polymorphism within the TLR2 gene as a risk factor [33]. In this study, we selected 35 SNPs within 22 genes involved in the development of IE: IL1B, IL6, IL6R, IL8, IL10, IL12B, IL12RB, TNF, CRP, APOB, APOE, LIPC, LPA, NOTCH1, VDR, CASR, OPG, CALCR, F2, F5, F7, and ITGB3. Previous studies demonstrated the elevated serum levels of IL-1β, IL-6, IL-8, IL-10, IL-12, TNF-α, and CRP in patients with IE compared to the healthy blood donors which indicates the possible importance of these cytokines in the clinical course of IE; however, the exact role of these inflammatory molecules in IE remains elusive [11, 34]. Apolipoproteins B and E, lipoprotein (a), and hepatic lipase are involved in the metabolism of lipids that can be important for IE development since patients with IE have lower level of serum high-density lipoprotein cholesterol (HDL) than healthy blood donors; furthermore, low serum HDL level is indicative of a complicated IE course [16]. Another well-established risk factor of IE is heart valve calcification, with NOTCH1, vitamin D receptor, calcium-sensing receptor, osteoprotegerin, and calcitonin receptor being the major regulators of serum calcium and phosphorus levels [27, 35, 36]. Finally, patients with IE are prone to thromboembolism due to increased systemic coagulation, activation of platelets, and impaired fibrinolysis [13, 14]. F2, F5, F7, and integrin beta 3 all are crucial proteins responsible for the maintenance of hemostasis [14, 27].

Here, we found that the G/A genotype of the rs1143634 polymorphism within the IL1B gene, the G/T genotype of the rs3212227 polymorphism within the IL1B gene, the A/G genotype of the rs1130864 polymorphism within the CRP gene, the A/G genotype of the rs13209079 polymorphism within the NOTCH1 gene, and the G allele of the rs1801197 polymorphism within the CALCR gene were associated with a decreased risk of IE whereas the T/T genotype of the rs1205 polymorphism within the CRP gene was associated with a higher risk of IE. Recent studies by Weinstock et al. [37] and Giannitsioti et al. [38] revealed that the SNPs within the IL1B, IL6, and TNF genes can be associated with IE; however, we did not confirm these findings with regard to IL6 and TNF. Small sample sizes, sample differences (e.g., age, gender, ethnicity, and clinical features), and geographical variations in the microbial causes of IE [39, 40] may be responsible for these discrepancies. Since all the SNPs in our study were in Hardy-Weinberg equilibrium, genotyping errors were unlikely to affect the results.

The G/A genotype of the rs1143634 polymorphism within the IL1B gene and the G/T genotype of the rs3212227 polymorphism within the IL12B gene were associated with a higher plasma level of IL-1β and IL-12 that may provide an insight into their possible protective role. It has been reported that both cytokines are abundant in the serum of the patients with IE compared to those with other infections [34]; one can explain this as a specific immune response to the bacterial or fungal infection of the heart valves or chambers. We suggest that IL-1β and IL-12 can limit the infection, preventing further progression of IE. However, we did not find the associations of two SNPs within the CRP gene reaching statistical significance with CRP plasma level, although it is also known to be higher in patients with IE compared to other subjects [11]. Other SNPs within the TNF-α, IL-6, IL-8, and IL-10 genes did not show a predictive
value and did not correlate with altered levels of the corresponding cytokines.

Our study has a number of limitations. First, the sample size is relatively small due to the low incidence rate of IE; however, this is a common drawback of genetic association studies on IE. With our sample size (123 cases and 300 controls), we had at least 83% and 99.7% power to detect odds ratio (OR) = 2 and OR = 3, respectively, with 5% alpha risk. Unfortunately, it was still impossible to analyze the genetic associations with the features or severity of IE. Second, technical difficulties made it unable to collect information on the potential confounders, that is, alcohol consumption, smoking status, and so forth. Third, we could not properly assess the microbiological profile due to extensive antibiotic therapy of IE at the district hospitals prior to the admission to our clinic. Finally, this study included only those patients requiring surgical treatment, as other patients with IE are not admitted to our clinic due to peculiarities of Russian healthcare.

5. Conclusions

Inherited variation within the cytokine, acute phase response, and calcium metabolism genes can be linked to IE, providing additional insight into its pathogenesis. In particular, heterozygous genotypes of the rs1143634 and rs3212227 polymorphisms are associated with both decreased risk of IE and higher level of IL-1β and IL-12, respectively, suggesting their possible importance. Further studies are needed to confirm our findings and for the further understanding of the genetic susceptibility to IE.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors’ Contributions

Anastasia V. Ponasenko, Anton G. Kutikhin, Leonid S. Barbarash, and Arseniy E. Yuzhalin designed the research. Anastasia V. Ponasenko, Natalia V. Rutkovskaya, Natalia V. Kondyukova, Yuri N. Odarenko, and Yana V. Kazachek recruited the patients with IE. Arseniy E. Yuzhalin recruited the healthy controls. Anastasia V. Ponasenko, Maria V. Khutornaya, Anna V. Tsepokina, and Arseniy E. Yuzhalin isolated the DNA, performed the genotyping, and conducted the enzyme-linked immunosorbent assay. Anton G. Kutikhin carried out the statistical analysis. Anton G. Kutikhin and Arseniy E. Yuzhalin wrote the paper. All the authors have read and approved the final article.

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