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Association between HMGCR, CRP, and CETP gene polymorphisms and metabolic/inflammatory serum profile in healthy adolescents

Benedetta Perrone[1], Paola Ruffo[1], Giuseppina Augimeri[1], Diego Sisci[1,2], Maria Stefania Sinicropi[1], Giovanni Tripepi[3], Corrado Mammì[4*†], Daniela Bonofiglio[1,2†] and Francesca Luisa Conforti[1,2*†]

Abstract

Background The complex interplay between health, lifestyle and genetics represents a critical area of research for understanding and promoting human well-being. Importantly, genetics plays a key role in determining individual susceptibility to disease and response to lifestyle. The aim of the present study was to identify genetic factors related to the metabolic/inflammatory profile of adolescents providing new insights into the individual predisposition to the different effects of the substances from the environment.

Methods Association analysis of genetic variants and biochemical parameters was performed in a total of 77 healthy adolescents recruited in the context of the DIMENU study.

Results Polymorphisms of 3-hydroxy-3-methylglutaril coenzyme A reductase (*HMGCR*; rs142563098), C-reactive protein gene (*CRP*; rs1417938, rs1130864), cholesteryl ester transfer protein (*CETP*; rs5030708), interleukin (*IL)—10* (IL-10; rs3024509) genes were significantly associated ($p < 0.05$) with various serum metabolic parameters. Of particular interest were also the correlations between the *HMGCR*polymorphism (rs3846663) and tumor necrosis factor (TNF)-α levels, as well Fatty-acid desaturase (*FADS*) polymorphism (rs7481842) and IL-10 level opening a new link between lipidic metabolism genes and inflammation.

Conclusion In this study, we highlighted associations between single nucleotide polymorphisms (SNPs) and serum levels of metabolic and inflammatory parameters in healthy young individuals, suggesting the importance of genetic profiling in the prevention and management of chronic disease.

Keywords Health, SNP, Lipid profile, Inflammation, Metabolic parameters, Statin

†Corrado Mammì, Daniela Bonofiglio and Francesca Luisa Conforti Senior last authors.

*Correspondence:
Corrado Mammì
corradomammi@tiscali.it
Francesca Luisa Conforti
francescaluisa.conforti@unical.it
Full list of author information is available at the end of the article

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Introduction

The immune system plays a vital role in our body's response to infection, injury, and disease. Therefore, inflammation is an essential immune response that can be activated when the body detects the presence of pathogens or tissue damage. While inflammation is a protective and necessary mechanism for healing, a persistent or low-grade inflammatory profile can contribute to the development of many chronic diseases, including cardiovascular diseases (CVDs), autoimmune disease, type 2 diabetes, and even some forms of cancer [1]. Lipid metabolism, on the other hand, plays an essential role in modulating inflammation in acute and chronic diseases [2]. There is considerable evidence that dietary and endogenous lipids possess pro- and anti-inflammatory properties, while lipoprotein profiles and composition modulate atherogenic and immunomodulatory pathways in chronic metabolic and inflammatory disorders such as obesity, cardiovascular, autoimmunity, and infectious diseases [3–5].

Recent studies have also reported that cytokines can influence blood cholesterol levels and their distribution in adipose tissue, thus contributing to the development of CVDs, obesity and other related pathologies [6].

In recent years, several studies have revealed an important link between the inflammatory profile and genetic factors. In fact, our genes can influence the body's inflammatory response, determining susceptibility to certain inflammatory diseases and the extent of the immune response [7].

Genetic factors influencing the inflammatory profile may be diverse, including genes encoding inflammatory cytokines, cytokine receptors [8], enzymes involved in the metabolism of inflammatory agents, and transcription factors [9] that regulate gene expression in the context of inflammation [10], thus contributing to individual predisposition to inflammatory diseases.

Some studies have also suggested that the combination of different single nucleotide polymorphisms (SNPs) on the genes of various inflammatory molecules, such as interleukins [11–13] as well as molecules involved in brain metabolism, such as Vascular Endothelial Growth Factor (VEGF) [14, 15], show an additive effect. Moreover, high levels of interleukin (IL) -6 (IL-6), major proinflammatory cytokines, are found in the plasma of obese subjects, and the related − 174G > C polymorphism (rs1800795) upstream of the transcription start site of the gene has been associated with insulin sensitivity and plasma triglyceride levels [16]. Furthermore, SNPs in *IL-1β* and *IL-10*, pro-inflammatory and anti-inflammatory cytokines respectively, have been reported to cooperate in many viral and infectious diseases including hepatitis B [17], influenza, and pneumonia [18–21] SNPs have also been described in *transforming growth factor beta 1* (*TGFβ1*) and heart disease [20, 21].

Of note, the *CRP*, which encodes a pentameric protein synthesized by the liver, is a sensitive marker of inflammation that is not only produced in response to pro-inflammatory cytokines such as IL-1 and IL-6, but is also present in the acute phase of inflammation [22, 23]. Likewise, genetic variants in *CRP*, rs3093068, rs1130864, rs1205, have been identified in correlation with CRP concentrations [24] and previously in ischemic and haemorrhagic stroke (+ 1059G > C, + 1444C > T, − 757A > G, − 717 A > G, − 286C > T > A and + 2147C > T) [25].

Regarding the influence of genetic factors on the metabolic profile, our previous results have highlighted the importance of the role of lipoprotein lipase (*LPL)*, fibronectin type III domain containing protein 5 (*FNDC5)* and peroxisome proliferator-activated receptor gamma (*PPARγ)* gene polymorphisms as determinants of health [26]. Other studies have reported reduced levels of high-density lipoprotein cholesterol (HDL-C) and an increased risk of coronary artery disease caused by increased activity of the *CETP* gene activity [27]. Specifically, associations have been reported between two polymorphisms, rs708272 (G277A) and rs5882 (I405V), and the risk of vascular disease [28].

Similarly, SNPs of *HMGCR*, encoding the key enzyme in cholesterol homeostasis [29, 30], are also associated with lipid/lipoprotein traits (such as triglycerides, total cholesterol levels, and LDL) in different populations [31].

In this study, we used high-throughput technologies to investigate the impact of SNPs on the metabolic and inflammatory serum profile of healthy adolescents and to evaluate their potential as determinants of health.

Methods

Participants

A total of 77 healthy adolescents (11–14 years) were enrolled and studied, as previously described [26]. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University of Calabria, Italy (#5727/2018).

Genotyping

Genomic DNA was isolated from peripheral blood leukocytes, using the Wizard Genomic DNA Purification Kit (Promega), and quantified by using the NanoDrop spectrophotometer (NanoDrop™ One/OneC Microvolume UV–Vis Spectrophotometer (Thermo Fisher Scientific).

NGS analysis was performed using a targeted panel, including genes and polymorphisms related to diet, lifestyle, and physical performance/sports, on the Ion S5 sequencer (Thermo Fisher Scientific), as previously reported [23].

Data analysis
Sequencing data generated from NGS experiments were analysed to identify single-nucleotide variants. The Torrent Suite™ (v5.12) Software (Thermo Fisher Scientific) was used for quality and coverage analysis, alignment against the GRCh37/hg19 human reference genome, and variant calling. "Germline-Low Stringency" was set as Variant Caller Parameters and annotated variants were filtered out by the following criteria: variant quality (QUAL) < 20, genotype quality (GQ) < 5, flow read space depth (FDP) < 6 and flow space alternate allele observations (FAO) < 2 [26, 32].

Variant frequencies were compared in 1000 Genomes (https://www.broadinstitute.org/) and GnomAD (https://gnomad.broadinstitute.org/) databases. Only variants with minor allele frequency (MAF) > 0.01 in each ancestry individually were included in the comparison.

The association between significant SNPs and metabolic and inflammatory variables was assessed by linear regression analysis using Tassel 5.2.21v. Non-parametric tests (Fisher's exact test and Chi-squared) were used to evaluate important pair correlations, also applying Bonferroni's correction. The squared of the determination coefficient (R^2) was calculated to estimate the proportion of the variability of dependent variable which was explained by the independent variables [33].

Covariates
Variables were described as mean and standard deviation, median and interquartile range (continuous variables) or number and percentage (categorical variables). We searched for the strength of the association between the occurrence of polymorphisms and a number of biochemicals variables using univariate linear regression analysislogistic regression analysis. The following variables were considered: circulating levels of IL-6, IL-10, TNFα, total bilirubin, and direct bilirubin. Multivariate logistic regression was also performed, testing all variables that were significantly associated with the dependent variable in univariate logistic regression. Linear regression models were used to estimate the regression coefficient (i.e., the mean increase in the dependent variable provided by each SNP) and 95% confidence intervals (CI) regarding the association independent and dependent variables. The Mann–Whitney test was used to identify differences in clinical parameters between cases and controls. All analyses were performed with the Statistical Package for Social Science (SPSS), version 24. A p–value ≤ 0.05 was considered statistically significant.

RegulomeDB analysis
To investigate a functional context for variants or regions of interest, particularly relevant for polymorphisms located in non-coding regions, we used RegulomeDB (https://regulomedb.org/regulome-search/). This is a software based on the system of prioritization of functional SNPs identifying their presence in a DNAase hypersensitive site or a transcription factor binding site. The SNP that showed the strongest evidence of being regulatory was assigned a score of 1 and, the SNP that displayed the least evidence of being functional was marked as 6.

Results
NGS
We used a 13-gene NGS-based targeted resequencing. We detected 175 variants in 10 genes of interest (*IL-10, IL-6, IL-1β, TNFα, CETP, HMGCR, TGFB1, CRP, homeostatic iron regulator—(HFE), FADS*). The filtering of annotated variants was previously reported in our paper [26]. In line with the aim of this study, to identify variants with high frequency in the population, variants with MAF < 0.01 were filtered out.

Twenty-nine variants were detected, as shown in Table 1. Of these, 18 variants were located in the intronic region, 1 in the intergenic region and 7 in the flanking regions (6 in the 3'_UTR and 1 in the upstream region). The remaining 3 variants were exonic (1 synonymous and 2 missense substitutions).

Linear regression analysis
By the linear regression analysis, we evaluated the correlation between the identified SNPs and the levels of inflammatory markers and found 7 significant associations (P < 0.01 and/or P < 0.05) after Bonferroni corrections. Figure 1 shows the significant associations between SNPs and parameters related to inflammatory and lipid profiles.

Our analyses showed a statistical difference in the mean uric acid levels between the two allelic subgroups in HMGCR. In particular, the rs142563098-TC genotype showed a significantly lower acid uric level (22.5 ± 3.10 mg/dl) than the TT genotype group (22.5 ± 3.10 mg/dl). Of note, after data adjustment for age, sex and cat.BMI, a positive association was observed between TNF-α levels and HMGCR/rs3846663-CT genotype, and increased levels of IL-10 in the presence of FADS/rs7481842-CG genotype (Table 2). We list the odds ratios derived from the individual analysis along with their 95% CIs and corresponding p-values for the 2 SNPs.

Table 1 SNPs identified in targeted genes

Name/Gene ID	Description	Chromosomal location	SNPs	GnomAD/1000Genome	Ref Allele	Alt Allele	Location
IL-10	*Interleukin 10*	1:206,767,602–206,774,541	rs1518111 rs1554286 rs3024509	0.29/0.42 0.26/0.40 0.04/0.02	T A A	C G/T G	Intron variant Intron variant Intron variant
IL-6	*Interleukin 6*	7:22,766,819–22,771,617	rs1800795	0.29/0.14	C	G/T	Intron variant
IL-1β	*Interleukin 1 beta*	2:112,829,751–112,836,816	rs1071676 rs1143627 rs1143633 rs1143634 rs1143639	0.19/0.13 0.44/0.47 0.30/0.31 0.19/0.13 0.19/0.13	C G C G C	G A A/G/T A T	3_Prime UTR variant Upstream variant Intron variant Exonic variant Intron variant
TNF-α	*Tumor Necrosis Factor-Alpha*	6:31,575,565–31,578,336	rs3093662 rs3093664 rs3093665	0.07/0.07 0.07/0.07 0.02/0.02	A A A	G G C	Intron variant Intron variant 3_Prime UTR variant
CETP	*Cholesteryl Ester Transfer Protein*	16:56,961,923–56,983,845	rs708272 rs5030708	0.38/0.37 0.02/0.01	G C	A/C T	Intron variant Intron variant
HMGCR	*3-Hydroxy-3-Methylglutaryl-CoA Reductase*	5:75,336,329–75,364,001	rs10474435 rs10515198 rs11742194 rs12916 rs142563098 rs3846662 rs3846663 rs5909	0.01/0.01 0.08/0.07 0.08/0.07 0.36/0.41 -/0.01 0.42/0.37 0.34/0.40 0.08/0.07	T G C T T A C G	C A T A/C/G A/C G/T T A	3_Prime UTR variant Intron variant Intron variant 3_Prime UTR variant Intron variant Intron variant Intron variant 3_Prime UTR variant
TGFB1	*Transforming growth factor beta 1*	19:41,330,323–41,353,922	rs1800471 rs1800472 rs8179181	0.08/0.04 0.02/0.01 - / 0.07	C G G	G/T A A/C/T	Exonic variant Intron variant Exonic variant
CRP	*C-Reactive Protein*	1:159,682,079–159,684,379	rs1130864 rs1205 rs1417938	0.26/0.20 0.30/0.33 0.25/0.19	G C T	A T A/C	Intron variant 3_Prime UTR variant Intron variant
FADS	*Fatty Acid Desaturase*	11:61,799,627–61,829,318	rs7481842	0.13/0.09	C	G/T	Intergenic variant

Key: Chr: chromosome; Ref: reference; Alt: alternative

In addition, the IL-10/rs3024509-AG genotype was associated with increased low-density lipoprotein (LDL) (82 ± 20 vs 100 ± 29) and total cholesterol (147 ± 23 vs 170 ± 43) concentrations; however, we did not observe the same difference after adjustment for sex, age and cat.BMI. Furthermore, cholesterol and LDL levels were significantly increased in the presence of the CETP/rs5030708-CT genotype (180 ± 47 vs 149 ± 25 and 111.75 ± 39 vs 83.6 ± 20.7). Likewise, CRP/rs1417938-TA and CRP/rs1130864-GA genotypes were significantly correlated with higher fasting glucose levels (81.6 ± 7.26 vs 78.9 ± 5.89 and 81.25 ± 7.17 vs 78.9 ± 5.87, respectively).

In order to understand whether the identified polymorphisms in non-coding regions have functional consequences, we evaluated their impact through RegulomeDB ranks. Data retrieved from this software showed that most of the identified SNPs have a probable regulatory role, with a ranking between 1 and 5 for all except one (Table 3).

Discussion

The present study analysed the association between serum metabolic/inflammatory parameters and the occurrence of polymorphisms in a sample of healthy adolescents from Southern Italy. In detail, we have identified a new genetic polymorphism in the HMGCR gene, rs142563098 associated with acid uric. Several studies have suggested that serum uric acid is correlated with CVD, but some studies have reported contradictory results. However, recent meta-analyses of prospective studies have supported that hyperuricemia is an independent risk factor for CVDs [34–36].

It has demonstrated, also, that uric acid induces reactive oxygen species (ROS) production and it activates several intracellular signalling pathways that result in the production of inflammatory cytokines, adhesion factors, and chemokines regulating cell proliferation and apoptosis and in turn leading to atherosclerosis development [37].

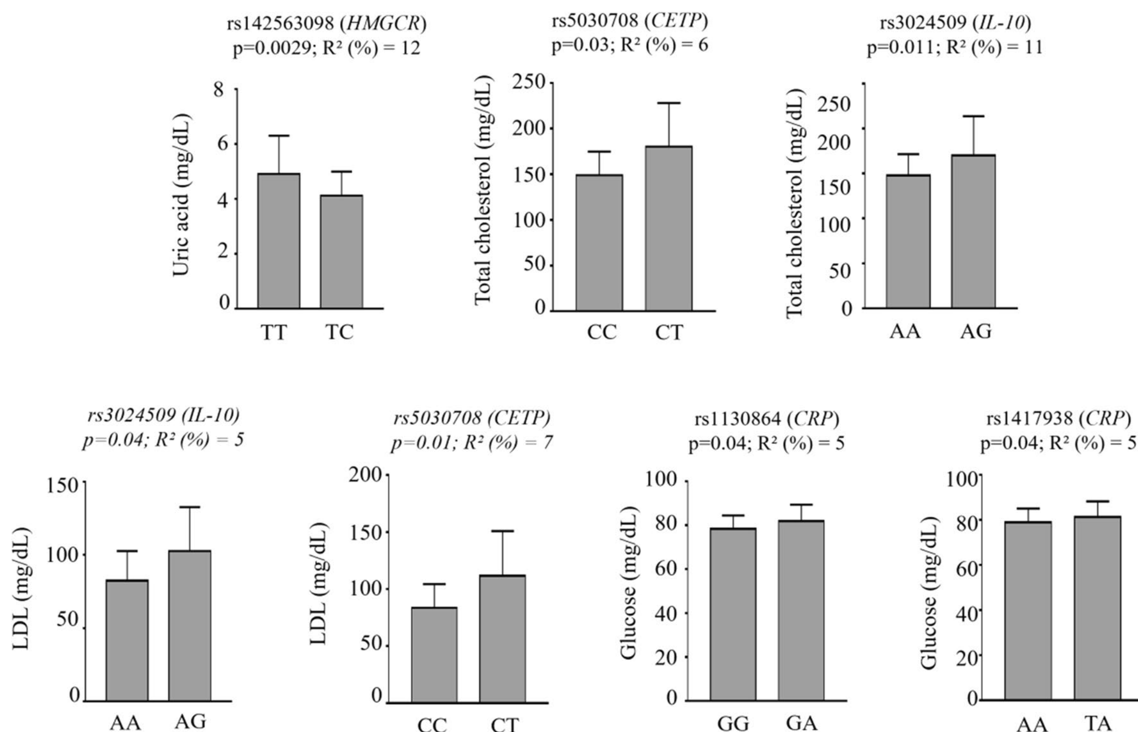

Fig. 1 Significantly associated SNPs with inflammatory markers in our cohort. The X-axis indicates the genotype status. R2: is the statistic used for association analyses and p is the Benjamini–Hochberg adjusted p-value

Table 2 Associations of polymorphisms in the *HMGCR* and *FADS* genes with TNF-α and IL10 levels

Gene	SNP ID	Minor Allele	Risk genotype	Serum concentration effect	*Mean increase	(95% CI)	*p*-value
HMGCR	rs3846663	T	CT	↑TNF-α	+0.49	0.05–0.92	0.033
FADS	rs7481842	C	CG	↑IL-10	+1.09	0.34–1.85	0.006

SNP, Single Nucleotide polymorphism; CI, confidence interval.

*Derived from the slope of the linear regression analysis

Interestingly, in our cohort, we found increased serum TNF-α levels in the presence of the *HMGCR*/rs3846663 T allele ($p < 0.05$). This polymorphism has previously been identified in genome-wide association (GWA) studies as being associated with increased LDL-cholesterol (LDL-C) levels [31, 38]. Although the presence of the *HMGCR* variants is already known and associated with lipid profile, we have shown for the first time the involvement of SNPs of this enzyme in inflammatory status.

Statins are a well-established family of drugs that lower cholesterol levels via the competitive inhibition of the HMGCR enzyme. Statins also have anti-inflammatory effects, including reducing CRP concentrations [39]. Furthermore, statins reduce TNF-α and interferon gamma (INFγ) production in stimulated T-lymphocytes and inhibit the T helper cell (Th-1) immune response [40]. Addition of statins to human hepatocytes reduces CRP levels induced by circulating IL-6, suggesting that the anti-inflammatory effects of statins are hepatic in nature [41].

These effects of statin treatment are most likely not indirect and mediated by decreased cholesterol levels, but rather direct and could be due to decreased protein prenylation, another HMGCR-dependent reaction. Protein prenylation is a posttranslational modification of proteins, which results in the covalent modification of these proteins with the mevalonate pathway intermediates as farnesyl pyrophosphate or geranylgeranyl pyrophosphate. The lipophilic prenyl groups enable proteins to anchor to cell membranes or facilitate protein–protein interactions.

Table 3 List of the non-coding SNPs and related RegulomeDB scores

dbSNP IDs	Chromosome location	Rank	Score
rs3846663	chr5:74655725–74655726	1f	0.55324
rs3024509	chr1:206943296–206943297	3a	0.55134
rs5030708	chr16:56996278–56996279	3a	0.47027
rs142563098	chr5:74633013–74633014	4	0.60906
rs1417938	chr1:159684185–159684186	5	0.58955
rs7481842	chr11:61639704–61639705	5	0.13454
rs1130864	chr1:159683090–159683091	7	0.18412

RegulomeDb category summaries [33]. Rank refers to the supporting evidence for that particular location or variant id. In general, if more supporting data is available, the higher is its likelihood of being functional and hence receives a higher score (with 1 being higher and 7 being lower score); 1b-1f: Likely to affect binding and linked to expression of a gene target; 2a-2c: Likely to affect binding; 3a-3b: Less likely to affect binding;4-5-6: Minimal binding evidence

The RegulomeDB probability score is ranging from 0 to 1, with 1 being most likely to be a regulatory variant

Important prenylated proteins include members of the Ras superfamily of small GTPases, such as Ras and Rho, involved in the proliferation and differentiation processes of cells [42]. The RhoA–NFκB interaction has been shown to be important in cytokine-activated NFκB processes, such as those induced by TNF-α [43, 44].

We also found increased serum levels of IL-10 in the presence of the *FADS* SNPs rs7481842, while a known correlation between polymorphisms in the FADS gene and serum lipids in GWA studies has been described previously [45]. However, no associations with anthropometric measures and lipid parameters were reported in our sample, probably due to the small size of the population studied. Fatty acid desaturase 1 and 2 (*FADS1* and *FADS2*, respectively) genes encode for key enzymes in the Polyunsaturated Fatty Acid (PUFA) metabolism, the δ-5 desaturase (D5D) and D6D, respectively [46]. In populations eating a Western diet rich in omega-6 PUFA, a high desaturase activity may promote increased bioavailability of arachidonic acid with a prevailing synthesis of arachidonic acid-derived proinflammatory eicosanoids, finally favoring atherosclerotic vascular damage. In contrast, high desaturase activity in subjects consuming a diet rich in omega-3 PUFA or receiving omega-3 PUFA supplementation could result in the opposite situation with a preferential synthesis of anti-inflammatory eicosanoids. For these reasons, people carrying specific *FADS* haplotype polymorphisms may be predisposed to more pronounced vascular inflammatory damage in the context of a Western diet, but also to an increased beneficial effect of omega-3 PUFA supplementation [46]. It is therefore also important to bear in mind that diseases are caused not only by genetic factors but also by a complex combination of environmental determinants. Another novel association was observed between the *CRP*/rs1417938 TA genotype and glucose levels ($p < 0.05$) in our study. Moreover, we also observed the relationship between the rs1130864-GA genotype and increased fasting glucose levels ($p < 0.05$), as previously reported [47]. Our findings, confirming the direct correlation between this gene and glucose homeostasis, further support the influence of genetic factors in metabolic profiles related to inflammation genes.

Moreover, in our study, analysis of the rs5030708 polymorphism in *CETP* showed a statistically significant increase of total ($p < 0.05$) and LDL cholesterol ($p \leq 0.01$) levels, which has never been reported in the literature. CETP is a glycoprotein that is synthesized in the liver and promotes bidirectional transfer of cholesteryl esters and triglycerides between all plasma lipoprotein particles: (i) transfer of cholesteryl esters from cholesteryl ester-rich HDL particles to LDL and very LDL (VLDL) particles and (ii) transfer of triglycerides from triglyceride-rich VLDL particles and chylomicrons to HDL and LDL particles. Thereby, CETP has a direct effect on both plasma HDL-C as well as LDL-C levels [48]. The *CETP* gene, located on chromosome 16q21, is highly polymorphic and polymorphisms in this gene have a differential effect on the HDL-C fraction. The importance of plasma CETP in lipoprotein metabolism was demonstrated by the discovery of CETP-deficient subjects with marked hyperalphalipoproteinaemia (HALP) [49]. When CETP is high, the efficiency of HDL to transfer triglycerides (TGs) is increased, leading to a reduction in TGs, HDL particles are rapidly cleared, and HDL-C levels are reduced [49]. Previous association studies have indicated that *CETP* polymorphisms are associated with lower HDL-C concentrations in children with a family history of diseases of the cardiovascular system [50]. Other results have shown that *CETP* SNPs interact with dietary carbohydrate intake on metabolic factors, such as hypertension, dyslipidaemia and, obesity. Specifically, a potential interaction between polymorphism in this gene and dietary fat on plasma lipid and lipoprotein concentrations has been reported [51, 52], suggesting that the CETP gene also plays a crucial role.

It is good to note that the role of non-coding variations of different genes has already been reported relating to inflammatory phenomena and several diseases. For example, IL-1B (-511C > T) has been reported to be associated with the severity and progression of multiple sclerosis (MS), while the NLRC4 rs479333 G > C variant has shown beneficial effects by limiting disease progression and supporting response to treatment with INF-β [53]. In addition, different human leukocyte antigen G (HLA-G) polymorphisms have been associated with distinct levels of HLA-G expression and with the development

of sepsis. Intronic SNPs in the PTNP2 gene have been associated with changes in PTPN2 expression and modulation of binding to important transcription factors. PTPN2 protein was overexpressed in inflamed intestinal tissue of patients with Chron's disease [54].

Overall, to the best of our knowledge, this is the first study showing novel associations between *HMGCR* , *CRP*, and *CETP* polymorphisms and serum metabolic and inflammatory parameters in healthy adolescents, indicating that these polymorphisms may act as risk factors influencing the metabolic/inflammatory profile in a young population. Disrupting the complex interplay between lipid and inflammatory profiles could be a strategy to limit the risk of the development of chronic diseases. In this context, among different molecules, statins are small inhibitors of cholesterol synthesis, able to alter proinflammatory metabolic signatures to potentially lessen these disease pathogeneses [55]. In addition to this, it should be taken into account that, in the presence of certain genetic variants, the use of these pleiotropic molecules may positively impact the metabolic/inflammatory profile modifying the risk factors of related diseases, and thus confirming the relevance of genetics in personalized medicine. Although the limitation of our study is represented by the small size of our cohort which could make it difficult to generalize the data, the present results emphasize the importance of genetic profiling as a determinant of health. Further research is needed to validate these findings in a larger population and to explore the underlying mechanisms involved.

Abbreviations

SNPs	Single nucleotide polymorphisms
HMGCR	3-Hydroxy-3-methylglutaryl-coenzyme A reductase
VEGF	Vascular endothelial growth factor
CRP	C-reactive protein (CRP)
CETP	Cholesteryl ester transfer protein
IL	Interleukin
TGFβ1	Transforming growth factor beta 1
HDL-C	High-density lipoprotein cholesterol
QUAL	Variant quality
GQ	Genotype quality
FDP	Flow space read depth
FAO	Flow space alternate allele observations
MAF	Minor allele frequency
GLM	General linear model
OR	Odd ratios
CI	Confidence intervals
Chr	Chromosome
LDL	Low-density lipoprotein
TNF-α	Tumor necrosis factor alpha
INFγ	Interferon gamma
HALP	Hyperalphalipoproteinaemia
TG	Trygliceride

Author contributions

Conceptualization, FLC, DB, BP and CM and BP; methodology, BP, PR, DS, GA and GT; validation, BP and PR; formal analysis, BP, GT and GA; investigation, BP; resources, DB,FLC and SS; data curation, BP and FLC; writing—original draft preparation, BP and FLC; writing—review and editing, BP, FLC, DB and CM; visualization, BP, GA and PR; supervision, DB, FLC and CM; funding acquisition, DB, FLC, SS and CM. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The data presented in this study are available in results.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University of Calabria.

Consent for publication

Informed consent was obtained from all subjects involved in the study for research purposes.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential competing interests.

Author details

[1]Department of Pharmacy and Health and Nutritional Sciences, University of Calabria, Rende, CS, Italy. [2]Centro Sanitario, University of Calabria, Via P Bucci, Rende, CS, Italy. [3]Institute of Clinical Physiology of Reggio Calabria, IFC-CNR, Reggio Calabria, Italy. [4]Great Metropolitan Hospital BMM, Reggio Calabria, Italy.

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