

Endothelial Lipase RS3744843 Polymorphism and Lipid Profile in Behçet's Disease Patients

Polymorphisme RS3744843 de la lipase endothéliale et profil lipidique chez les patients atteints de la maladie de Behçet

Rihab Makhoul^{1,2}, Meriam Messedi², Mouna Snoussi³, Khansa Chaabouni^{1,2}, Bochra Ben Rhouma⁴, Zouhair Bahloul^{2,3}, Fatma Makni Ayadi^{1,2}, Kamel Jamoussi^{2,5}

1. Department of Clinical Chemistry Laboratory, Habib Bourguiba Hospital, Sfax, Tunisia
2. Research Laboratory LR19ES13 of Molecular Bases of Human Diseases, Faculty of Medicine of Sfax, Sfax, Tunisia
3. Department of Internal medicine, Hedi Chaker Hospital, Sfax, Tunisia
4. Department of Human Molecular Genetic Laboratory, Faculty of Medicine of Sfax, Sfax, Tunisia
5. Department of Clinical Chemistry Laboratory, Hedi Chaker Hospital, Sfax, Tunisia

ABSTRACT

Introduction: Endothelial lipase gene (LIPG) is implicated in lipid metabolism particularly HDL-C metabolism and in inflammation. Several identified single nucleotide polymorphisms (SNPs) of LIPG were associated with lipoprotein and apolipoprotein metabolism. The implication of LIPG in a chronic inflammation due to multisystemic vasculitis has not been elucidated.

Objective: To assess the association between EL 2037 T/C (rs3744843) polymorphism and alterations in lipid profiles and biomarkers of endothelial dysfunction (such as high-sensitivity C-reactive protein and Homocysteine) in Tunisian patients with Behçet disease (BD).

Methods: A case-control study including BD patients with controls was performed. Lipid profile, high-sensitivity C-reactive protein and homocysteine were assessed to all subjects. The polymerase chain reaction-restriction fragment length polymorphism method was used.

Results: We included 116 BD patients and 102 healthy controls in this study. Overall, HDL-C levels were significantly lower in patients. While genotype and allele distributions did not differ significantly between groups, a distinct pattern emerged in HDL-C levels. In healthy controls, C allele carriers had higher HDL-C concentrations compared to TT individuals. In contrast, BD patients carrying the C allele had significantly lower HDL-C levels, particularly in the presence of hyperhomocysteinemia or a disease activity score >5.

Conclusion: EL 2037 T/C polymorphism was correlated with lipid levels in BD patients and controls. No association was demonstrated between this polymorphism and BD.

Keywords: Endothelial Lipase, Polymorphism, Lipid profile, Inflammation, Behçet's disease, Multisystemic vasculitis

RÉSUMÉ

Contexte : Le gène de lipase endothéliale (LIPG) est impliqué dans les modifications du profil lipidique, en particulier le métabolisme du HDL-C et dans l'inflammation. Plusieurs polymorphismes à nucléotide unique (SNP) identifiés de LIPG étaient associés au métabolisme des lipoprotéines et apolipoprotéines. L'implication du LIPG dans une inflammation chronique due à une vascularite multisystémique n'a pas été élucidée.

Objectif : Évaluer l'association entre le polymorphisme EL2037T/C(rs3744843) et les altérations des profils lipidiques et des biomarqueurs de dysfonction endothéliale (CRP à haute sensibilité à la protéine C réactive, homocystéine) chez les patients tunisiens atteints de la maladie de Behçet (TB).

Méthodes : Une étude cas-témoins incluant des patients atteints de trouble bipolaire avec des témoins a été réalisée. Le profil lipidique, la CRP et l'homocystéine ont été évalués à tous les sujets. La méthode de polymorphisme de longueur des fragments de restriction par réaction en chaîne par polymérase.

Résultats : Nous avons inclus 116 patients atteints de trouble bipolaire et 102 contrôles sains dans cette étude. Les fréquences de TT. Les génotypes TC et CC étaient respectivement : 90,52 %, 8,62 % et 0,86 % dans le groupe témoin contre 89,21 %, 10,78 % et 0 % dans le groupe BD. Nous n'avons pas trouvé de différences significatives entre le groupe BD et le groupe témoin pour les distributions génotypique et allélique. Les niveaux de HDL-C étaient significativement plus faibles chez les patients. Les porteurs témoins de l'allèle C présentaient des niveaux de HDL-C plus élevés que dans le génotype TT. Les patients BD porteurs de l'allèle C présentaient des niveaux de HDL-C plus faibles que dans le génotype TT. Les patients atteints de TB porteurs de l'allèle C présentaient des niveaux plus faibles de HDL-C en présence d'hyperhomocystéinémie ou d'un score d'activité de la maladie supérieur à 5.

Conclusion : Le polymorphisme EL2037T/C a été corrélé avec les niveaux lipidiques chez les patients bipolaires et chez les témoins. Aucune association n'a été démontrée entre ce polymorphisme et BD.

Mots clés: Lipase endothéliale, polymorphisme, profil lipidique, inflammation, maladie de Behçet, vascularite multisystémique

Correspondance

Rihab Makhoul

Department of Clinical Chemistry Laboratory, Habib Bourguiba Hospital, Sfax, Tunisia

Email: makhoulrihab@yahoo.fr

INTRODUCTION

Behçet's disease (BD) is notably prevalent in Tunisia, with an overall incidence rate of 10 per 10000 individuals (1,2). BD is a multisystemic vasculitis which characterized by recurrent oral and genital with ocular, skin, joint, vascular and nervous system manifestations (1,2,3). Concurrently, a chronic and recurrent inflammatory process, whose etiology remains elusive, often coexists. This inflammation is often associated with atherosclerosis and endothelial dysfunction (2,4), with lipid profile alteration manifesting, notably a reduction in plasma high-density lipoprotein cholesterol (HDL-C) (6). This decrease may be attributed to the implication of inflammatory mediators in altering the hepatic synthesis of regulatory proteins and/or the enzymes activities involved in lipid metabolism (1,3,7).

At least 50% of plasma HDL-C is genetically determined (8), with the endothelial lipase gene (LIPG) among the candidate genes. LIPG codes for endothelial lipase (EL) protein (EC 3.1.1.32), a member of the triglyceride lipase family synthesized by endothelial cells and other cell types such as macrophages and hepatocytes (9,10). EL has predominantly phospholipase A1 (PLA1) activity combined with minimal triglyceride lipase activity. It hydrolyzes serum HDL-C to low-lipid apolipoprotein (Apo) A1 and free fatty acids (11). This enzyme appears to be implicated in changes in lipid profile particularly HDL-C metabolism and in inflammation (6,12). Furthermore, a bidirectional relationship between the inflammatory process and EL expression has been established (6).

While several single nucleotide polymorphisms (SNPs) of LIPG have been associated with lipoprotein and apolipoprotein metabolism and with inflammation (12,16), their implication in BD, a chronic inflammatory multisystemic vasculitis, remains unexplored. Notably, the EL 2037 T/C polymorphism (rs3744843) has recently been studied, yielding controversial results (17–19). EL 2037 T/C appears to be linked to HDL-C levels, with the C allele potentially serving as a protective factor against coronary artery disease (17–19).

This study aims to investigate the hypothesis that the EL 2037 T/C polymorphism is associated with alterations in lipid profiles and biomarkers of endothelial dysfunction (such as CRP and Hcy) in Tunisian BD patients. We further propose that this association may be modulated by the chronic inflammatory status characteristic of the disease and the potential involvement of this polymorphism in the pathophysiology of BD.

METHODS

Study subjects

It was a case-control study, comparing BD patients with a healthy control group. BD patients were recruited from the Department of Internal medicine at Hedi Chaker University Hospital of Sfax. Diagnosis of BD was established according the classification criteria for Behçet's disease, proposed by the International Study Group for Behçet's Disease (20). Patients were aged between 20 and 65

years without other associated chronic inflammatory disease and family history of early cardiovascular disease. In this study, the disease duration was not considered as a selection criterion. We also recruited indiscriminately patients in periods of relapse and those in phases of remission. For the familial forms of BD, only one patient from these families (index case) was retained and the others were excluded. The control group consisted of unrelated, age- and geographically matched individuals, without personal or family history of inflammatory or cardiovascular disease. Controls were considered to be in good apparent health, defined as the absence of clinical signs of chronic illness, and confirmed by normal physical examination and routine laboratory screening. Controls in whom dyslipidemia and/or inflammation were discovered during biochemical analyzes (lipid disorders, increased CRP and/or fibrinogen) or any abnormal biochemical findings suggestive of subclinical disease were excluded. Controls were not related to each other or to the patients.

All controls and patients gave their informed consent to participate in the study.

Clinical assessments

We collected the clinical data on: Age, medication history, the body mass index (BMI), the clinical manifestation and the disease activity score for BD (BDAI) at the time of study. BDAI score was calculated as previously reported (21). Patients with BDAI score greater than 5 were considered to have active disease.

Laboratory analysis

Following 12-hour fast, venous blood samples were collected into a lithium heparin tube and two ethylene diamine tetra-acetic acid (EDTA) tubes for biochemical analysis and genomic DNA extraction respectively.

• Biochemical analysis:

Total cholesterol (TC), triglyceride (TG) and HDL-C were detected by enzymatic methods. Levels of LDL cholesterol (LDLc) were calculated using the Friedewald method. High-sensitivity C-reactive protein (CRP_{hs}) and homocysteine levels were also determined. Apolipoproteins (apoA1 and apoB) and lipoprotein Lp(a) were detected by immunoturbidimetric assays, only in patients. All of the biochemical measurements were analyzed by automatic biochemical analyzer Cobas 6000[®] analyzer; (Roche diagnostics, Germany).

Low HDL-C is defined by levels below the threshold of 1 mmol/L for men and 1.2 mmol/L for women (22). According to the Third Report of the National Cholesterol Education Program (NCEP), LDL-C/HDL-C ratio of 2.5 is associated with an increased risk of coronary artery disease (23). A CRP_{hs} greater than 3mg/L is predictive of a high risk of cardiovascular disease (24). Hyperhomocysteinemia is defined by a value greater than 15 µmol/L (25).

• Genotyping of EL polymorphism:

Genomic DNA was isolated from peripheral blood

leukocytes using standard phenol-chloroform extraction methods and was stored at -80°C. Genotypes were determined by using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. EL 2037 T/C polymorphism is located in exon 10 at the 3'UTR region. It is a transition (T/C) at the position 2037. The size of the amplified sequence is 641 bp. Amplification of the fragment was performed by using forward primer (F: 5'-GTT ACT GCT GAG GAC CCA C-3') and reverse primer (R: 5'-CAGTGGAGTTGGGATTCTA-3') and Taq DNA polymerase (Thermoscientific). Amplification reaction conditions were: denaturation for 2 min at 95°C, followed by touch-down PCR [initial 14-cycle loop repeated 3 times—95°C for 30 s, 62°C for 30 s (–0.5°C every cycle), 72°C for 70 s], followed by 19 cycles of 95°C for 30 s, 54.1°C for 30 s, and 72°C for 70 s, and then incubation at 72°C for 5 min. The PCR product was digested with restriction enzyme SmaI (Fly Cut®) according to the manufacturer's instructions. The digested PCR product was separated by 1.5 % agarose gel electrophoresis and visualized under ultraviolet light. To confirm the genotyping results, a part of PCR products was sent for sequencing at the department of genetic medicine.

Statistical analysis

All statistical evaluations were analyzed by using SPSS software (version 20.0, SPSS Inc., Chicago, Illinois, USA). The Hardy-Weinberg equilibrium (HWE) was assessed using the Chi-square test. Continuous variables were represented as means $\pm$ standard deviation (SD) and compared by using independent-sample t-tests. Qualitative variables including genotype and allele frequencies were reported as frequencies and percentages, and assessed by Chi-square test. A p-value less than 0.05 was considered as statistical significance.

RESULTS

Clinical and biochemical characteristics

We included 116 BD patients and 102 in this study. The comparison of age, sex ratio and BMI between the two populations did not reveal any significant difference. The two groups were therefore matched for these three variables. The table 1 compares clinical characteristics and biochemical analysis results of the two groups. BD patients had higher CRPus and homocysteine levels than controls. Mean HDL-C levels were significantly lower in patients ($p=0.039$), while no significant difference was found for the other lipid parameters between the two groups. Notably, the LDL-C/HDL-C ratio in BD patients was greater than 2.5 and significantly higher than in controls. When stratifying BD patients by hs-CRP levels (>3 mg/L) or by hyperhomocysteinemia (Hcy >15 μ mol/L), no significant differences in the overall lipid profile were observed (data not shown).

Table 1. Clinical and biochemical characteristics between BD patients and controls

	BD group (n=116)	Control group (n=102)	p
Age (years)	48.7 (22.8-54.6)	41.1 (21.7-45.9)	0.1
Sex-ratio H/F	78/38	61/41	0.27
BMI (kg/m ²)	25.1 (18.9-27.1)	25.5 (19.3-28.1)	0.7
TC (mmol/L)	4.79 $\pm$ 0.92	4.67 $\pm$ 1.01	0.426
TG (mmol/L)	1.31 $\pm$ 0.69	1.17 $\pm$ 0.66	0.148
HDL-C (mmol/L)	1.16 $\pm$ 0.32	1.26 $\pm$ 0.31	0.039
LDL-C (mmol/L)	3.02 $\pm$ 0.79	2.86 $\pm$ 0.85	0.241
LDL-C/HDL-C	2.83 $\pm$ 1.35	2.39 $\pm$ 0.85	0.023
CRP us (mg/L)	5.3 $\pm$ 10.01	1.74 $\pm$ 1.46	0.002
Homocysteine (μ mol/L)	14.11 $\pm$ 9.59	11.75 $\pm$ 3.92	0.031

BD: Behçet's disease; BMI: Body mass index; TC: Total cholesterol; TG: Triglyceride; CRPus: High-sensitivity C-reactive protein; Hcy: Homocysteine;

EL 2037T/C polymorphism, lipid profile and endothelial dysfunction markers

The genotypic frequencies were in accordance with HWE in both controls and patients ($\chi^2=0.63$. $p = 0.42$). The genotypic frequencies of TT, TC and CC in all subjects were 89.8%, 9.72% and 0.46% respectively. The frequencies of TT, TC and CC genotypes were respectively: 90.52 %, 8.62 % et 0.86 % in the control group against 89.21%, 10.78% et 0 % in the BD group. Given the rarity of the CC genotype, TC and CC carriers were pooled for analysis as carriers of the C allele. The genotypic and allelic distributions of the EL 2037T/C are presented in Table 2. We did not find significant differences between BD group and control group either for the genotypic distributions ($p=0.783$) in the TT genotype and TC+CC genotype nor for the allelic distributions ($p=0.57$).

Table 2. The genotypic and allelic distribution of EL 2037 T/C polymorphism

EL 2037 T/C	Groups		χ^2	p	OR 95%IC
	Control group (%)	BD group (%)			
Genotypes					
TT	90.52 %	89.21%	0.076	0.783	0.883 [0.366-2.134]
TC	8.62 %	10.78%			
CC	0.86 %	-			
Alleles					
T	94.83 %	94.6 %	1.127	0.57	0.803 [0.333-1.935]
C	5.17%	5.39 %			

BD: Behçet's disease

No significant association was found between genotypes and clinical characteristics (Table 3).

Table 3. Association between clinical characteristics and genotypic and allelic distributions of EL 2037 T/C polymorphism

Clinical characteristics		Genotypes EL 2037T/C		χ^2	p	OR 95% IC
		TT	TC+CC			
Gender	F	89,5 %	10,5 %	0,061	0,806	0,85 [0,23-3,1]
	H	90,9 %	9,1 %			
Vascular manifestations	No	91,2 %	8,8 %	0,065	0,799	1,203 [0,29 -5]
	Yes	89,7 %	10,3%			
Nervous system	No	89,8 %	10,2 %	0,608	0,436	0,439 [0,05 -3,67]
	Yes	95,2 %	4,8 %			
Ocular manifestations	No	90,5 %	9,5 %	0,022	0,881	0,897 [0,22 -3,7]
	Yes	91,4 %	8,6 %			
BDAI score	≤ 5	94,6 %	5,4 %	0,59	0,442	1,895 [0,36 - 9,9]
	>5	90,5%	9,5%			

BDAI: Disease activity score for Behçet disease

Table 4 compares lipid profiles within TT genotype and TC+CC genotype. In the overall study population, lipid profiles were not significantly different between EL 2037T/C genotypes. However, subgroup analyses, stratified by phenotype of disease, showed:

- Among controls, TC carriers had significantly higher HDL-C levels compared to TT individuals ($p = 0.038$).
- Among BD patients, TC+CC carriers had significantly lower HDL-C levels compared to TT carriers ($p = 0.041$).

In patients carrying the C allele, HDL-C was significantly lower when BD activity index (BDAI) > 5 ($p = 0.023$) and in patients with hyperhomocysteinemia ($p = 0.048$) (Table 5). The comparison of Apo A, Apo B and Lp (a) levels according to the genotypic distributions (TT vs. TC+CC) in BD patients, showed no significant difference (All $p > 0.05$).

Table 4. Effect of EL 2037T/C genotypes on lipid levels

	Genotype	TC	TG	HDL-C	LDL-C	LDL/HDL
All subjects	TT	4.73 ± 0.98	1.27 ± 0.69	1.21 ± 0.3	2.93 ± 0.83	2.6 ± 0.98
	TC+CC	4.82 ± 0.77	1.07 ± 0.53	1.19 ± 0.47	3.09 ± 0.75	3.1 ± 2.32
	p	0.772	0.237	0.911	0.494	0.419
BD Patients subgroup	TT	4.77 ± 0.94	1.33 ± 0.7	1.18 ± 0.31	2.98 ± 0.8	2.71 ± 1.05
	TC+CC	4.92 ± 0.73	1.15 ± 0.5	0.96 ± 0.39	3.3 ± 0.68	4.06 ± 2.85
	p	0.639	0.436	0.041	0.174	0.223
Control subgroup	TT	4.67 ± 1.02	1.19 ± 0.67	1.24 ± 0.29	2.87 ± 0.87	2.44 ± 0.86
	TC	4.68 ± 0.85	0.96 ± 0.59	1.49 ± 0.41	2.7 ± 0.71	2 ± 0.63
	p	0.982	0.363	0.038	0.709	0.202

BD: Behçet's disease; TC: Total cholesterol; TG: Triglyceride

Table 5. EL 2037T/C genotypes and endothelial dysfunction markers

Endothelial dysfunction markers	EL 2037 T/C genotypes	HDL-C (mmol/L)	p
CRP us <3 (n=81)	TT	1.18 ± 0.3	0.216
	TC+C	1.41 ± 0.31	
CRP us >3 (n=35)	TT	1.15 ± 0.25	0.494
	TC+C	0.97 ± 0.42	
Hcy <15 (n= 90)	TT	1.14 ± 0.29	0.371
	TC+C	1.04 ± 0.38	
Hcy > 15 (n=26)	TT	1.24 ± 0.3	0.017
	TC+C	0.64 ± 0,35	

High-sensitivity C-reactive protein (CRP)_{us} >3 mg/L: marker of high cardiovascular risk; Homocysteine (Hcy) >15 μmol/L: hyperhomocysteinemia

DISCUSSION

To the best of our knowledge, this is the first study to assess the association between the EL 2037 T/C polymorphism and lipid levels in Tunisian and North

African population and in patients with multisystemic vasculitis disease (BD). Our data showed that the EL 2037 T/C polymorphism was correlated with lipid levels in BD patients and healthy controls.

Acute and chronic inflammatory states are associated with changes in the lipid profile, in particular a decrease in HDL-C with alteration of its subfractions (26–29). These changes have also been previously reported in BD (30). Inflammation leads to decreased apoA1, an increased serum amyloid A, an increased EL and secretory phospholipase A2 activity, and decreased lecithin:cholesterol acyltransferase (LCAT) activity (29). In our study, comparing to control group, BD patients had significantly lower HDL-C levels and higher LDL-C/HDL-C ratio. Our results were consistent with the results of most previous studies (30–33).

Six SNPs with the potential to impact EL expression or activity levels, including both the promoter region (7410C/G, 7303A/C) and coding region (G26S, T111I, T298S and N396S), were particularly interesting (34).

The EL 2037 T/C polymorphism remains rarely studied in the literature (17–19). This SNP is located in the 3' untranslated region (3'UTR) of exon 10 at position chr18q21.1:49590804. The 3'UTR region would have an important role in the post-transcriptional regulation of gene expression and SNPs found in non-coding regions could have consequences for splicing, transcription factors and protein-protein interactions (35). SNPs studied in the 3'UTR region of the LDL receptor gene were significantly associated with plasma lipids (36). The SNP Rs4225 in the 3'UTR region of APOC3 was associated with HDL-C (37). Therefore, we hypothesized that the EL 2037 T/C polymorphism could have an effect in the post-transcriptional regulation on the activity of the enzyme and subsequently on the lipid metabolism. The present study showed that the EL 2037 T/C polymorphism

exists in the Tunisian population and that the genotypic distributions of this polymorphism were in accordance with the HWE. The frequency of the CC genotype and the C allele (5.32%) in our population was lower than in the Han Chinese population (17) and in the Japanese population (18) (Table 6). But this frequency was close to those estimated by the “Estonian”, “ALSPAC” and “TWINSUK” studies. Global minor allele “C” frequency (MAF) reported by Short Genetic Variations (dbSNP: the NCBI database of genetic variation) (<http://www.ncbi.nlm.nih.gov/SNP>) was between 4.2% and 12.4%. The disparity of genotypic and allele frequencies for this polymorphism could be explained by differences between the sample sizes, the ethnicities, the geographical origins and the complexity of the gene-environment interaction.

Table 6. Results of different studies about EL2037 T/C polymorphism

Study	Groups	Genotype (%)			P	Allele (%)		P	Effect on HDL-C	p
		TT	TC	CC		T	C			
Abudureyimu et al. (19) (China, 2021)	CAD	62.6	34.1	3.3	NS	79.6	20.2	NS	↗	0.008
	Healthy controls	64.6	30.3	5.1		79.6	20.4		↗	0.018
Gaojun Cai et al. (17) (China-Han, 2016)	CAD	62.89	33.14	3.97	0.011	79.4	20.5	0.004	=	NS
	Healthy controls	53.02	41.27	5.71		73.6	26.3		↗	0.016
Yamakaa kabayashi et al. (18) (Japan, 2003)	Healthy school children	57.64	34.7	7.64	-	75	25		=	NS
Our study (Tunisia 2021)	BD	90.52	8.62	0.86	NS	94.87	5.17	NS	↘	0.042
	Healthy controls	89.21	10.78	0		94.6	5.39		↗	0.038

CAD: coronary artery disease; BD: Behçet disease; NS: Non-significant; ↗ : increase ; ↘ : decrease ; = : no effect ;

In our study, when we analyzed association of the EL 2037T/C polymorphism with HDL-C in subgroups according to disease phenotype, we found a significant results. Among healthy controls, carriers of the C allele had higher mean HDL-C levels than in TT genotype carriers. In Cai et al. (17) and Abudureyimu et al. (19) studies, individuals with the C allele carriers genotype has higher Apo-A1 and HDL-C levels than in the TT genotype in the controls. We speculate that in healthy subjects, this SNP may reduce EL synthesis or decrease EL enzymatic activity in HDL-C metabolism, which may increase HDL-C levels since it has been demonstrated that EL levels were inversely correlated with HDL-C levels (15,38). We also suggested that this polymorphism could have a protective effect in healthy subjects. The C allele has been shown to be a protective factor against coronary artery disease (17).

Contrary to the control group, BD patients carrying the C allele had lower HDL-C levels. This contrasting effect suggest a disease-specific interaction between the EL 2037 T/C polymorphism and HDL-C metabolism. It is possible that in the inflammatory context of BD, the presence of the C allele exacerbates EL expression or activity, further decreasing HDL-C levels. Supporting this hypothesis, we observed that lower HDL-C levels were

found in the presence of hyperhomocysteinemia or BDAI score greater than 5 among C allele carriers. may Previous studies have shown that overexpression of EL has been associated with reduced HDL-C and apoA-I levels in several studies (9,39,40). In BD, this overexpression may be due to the associated inflammation, endothelial dysfunction and atherosclerosis. In fact, there is a positive correlation between EL activity and markers of inflammation (38). Pro-inflammatory cytokines, such as tumor necrosis factor and interleukin (IL)-1, upregulate EL expression by endothelial cells (41). Moreover, inflammation induces elevated EL expression across several tissues, including the aorta, lungs, heart, kidneys, liver and spleen (13). This upregulation by inflammation is one of the unique features of LIPG, unlike LPL and LH gene expressions which are downregulated by inflammatory cytokines (13). Therefore, an association between the studied polymorphism, low HDL-C levels and inflammation in BD could be then suggested.

However, we found no significant differences in either genotypic distributions or allelic distributions between patients and controls for this polymorphism. The genotypic distribution was also not correlated to sex, disease activity or severity.

These findings suggest that the EL 2037 T/C polymorphism is not directly involved in BD susceptibility, although it may modulate disease phenotype, particularly lipid metabolism, in affected individuals.

Several limitations of the current study should be considered. First, The sample size was relatively small and may have reduced the statistical power to detect modest genetic associations, particularly when analyzing less frequent genotypes such as CC. Due to the rarity of the CC genotype in our cohort, we grouped TC and CC carriers together for statistical analyses. Our results may suggest a potential protective role of the CC genotype, or alternatively, it could be an artifact of limited sample size. Larger studies are needed to confirm this observation and to enable separate analysis of the CC genotype. Additionally, functional assays are required to assess the impact of the polymorphism on EL mass, enzyme activity or post-transcriptional modification.

In conclusion, our data suggests that the EL 2037 T/C is associated with HDL-C levels in both BD patients and healthy individuals, with opposing effects depending on inflammatory status. Further studies are needed to validate these finding and to evaluate the association of this polymorphism with the endothelial dysfunction and the acceleration of the development of atherosclerosis in BD and vasculitides.

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