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ORIGINAL ARTICLE

Association analysis of polymorphisms in *EGFR*, *HER2*, *ESR1* and *THRA* genes with coronary artery diseases

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KEYWORDS

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Abstract *Background:* Research in the genetic basis of coronary artery diseases (CAD) has identified some genes and pathways associated with diseases that would not be considered to underlie conventional risk factors. Among these genes there are the EGFR (epidermal growth factor receptor) receptor family genes and the regulation factor genes (such as thyroid hormone receptor α (THRA) and estrogen receptor α (ESR1)).

Aim: In this study we investigated the relation between 4 polymorphisms within EGFR, HER2 (human epidermal growth factor receptor 2), ESR1 and THRA genes and CAD.

Subjects and methods: The association analysis was performed with 151 healthy individuals and 151 CAD patients documented by angiography.

Results: No significant difference was found in the allelic and genotypic frequency distribution of the four variants studied between the control and patient groups. We have also investigated the relationship of these polymorphic sites with clinical and biochemical parameters such as smoking habit, diabetes mellitus, hypertension, dyslipidemia, CAD severity, glucose, triglyceride, total cholesterol and urea levels. The EGFR and THRA variants were associated with glycemia and triglyceride levels, respectively. Also a significant correlation was found between the ESR1 polymorphism and the levels of urea and triglyceride.

Conclusion: Our results suggest the absence of any significant association between the four polymorphisms analyzed and CAD risk as well as disease severity.

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1. Introduction

Coronary artery disease (CAD) is a major cause of disability and premature death worldwide [1]. CAD is a multifactorial disease caused by genetic and environmental factors. Research in the genetic basis of CAD has opened new perspectives in the prevention and treatment of the common forms of this disease. Even, it has radically changed the concepts of some diseases origins. In fact, most of the genes that have been associated with CAD have primarily been involved in biochemical pathways related to what are considered conventional risk factors. However, recent genetic studies have begun to identify genes and pathways associated with CAD that would not be considered to underlie conventional risk factors [2]. Among these genes there are the EGFR receptor family genes and the regulation factor genes (such as thyroid hormone receptor (TRα) and estrogen receptor (ERα)).

The ErbB family (Erythroblastic leukemia viral oncogene homolog) is composed of four plasma membrane bound receptor tyrosine kinases, which are involved in molecular signaling related to cell growth and survival in many tumor types [3]. The human epidermal growth factor receptor 1, known as EGFR, is member of this receptor family. Previous studies suggested that genetic polymorphisms in the EGFR gene had been implicated in the susceptibility to some tumors [4] and inflammatory diseases. More recently, EGFR has been implicated in vascular pathophysiological processes associated with excessive remodeling and atherosclerosis [5,6]. Thereafter, polymorphisms of the EGFR gene have been associated with acute coronary syndrome [7], dilated cardiomyopathy [8], ischemic heart disease as well as arterial hypertension [9]. HER2 receptor is another member of EGFR family that has long been associated with breast cancer development and progression. Targeting the HER2 receptor is a milestone in the treatment of selected patients with early and advanced breast cancer [10,11]. Anticancer efficacy is complicated by a new type of heart failure [12–14]. There is evidence that trastuzumab (or Herceptin is an anti-HER2 humanized monoclonal antibody) [15,16], lapatinib (orally active drug for breast cancer which is a dual tyrosine kinase inhibitor interrupting the HER2 and EGFR pathways) [17], and pertuzumab (monoclonal antibody that inhibits the HER2 dimerization) [18] blocking the HER2-dependent signaling pathway may lead to the deterioration of left ventricular cardiac function.

The receptors for thyroid hormone (TRα) and estrogen (ERα) are prototypes of nuclear transcription factors that regulate the expression of target genes. These receptors are encoded by THRA and ESR1 genes, respectively and were found to be involved in CAD. In fact, thyroid receptors mediate the action of thyroid hormones that play multiple biological roles including effects on the cardiovascular system (lipid profile, blood pressure and cardiac output). Moreover, the expression of TRs is tissue-dependent and developmentally regulated [19] and TRα is expressed predominantly in the heart, bone, intestine, and brain. On the other hand, polymorphisms of the THRA gene have been associated with systolic blood pressure and hypertension risk [20].

Estrogen receptor α is mainly expressed in endothelial cells, vascular smooth muscle cells, and macrophages and plays an important role in vascular wall physiology and function [21]. Many studies have suggested that common single nucleotide polymorphisms (SNP) in the ESR1 gene have been associated with an increased risk of vascular diseases, such as arterial hypertension, cardiovascular diseases, alterations in serum lipid levels, and cerebrovascular disease [22–24]. More recently, it has been shown that genetic and epigenetic changes in the ESR1 gene may enhance plasma cholesteryl ester formation and lead to its low levels and thereby have been associated with cerebrovascular disease risk [25–27].

In this study, we report a case-control study in southern Tunisia, investigating the association between CAD and four genetic polymorphisms: R497K in the EGFR gene, I655V in the HER2 gene, T594T in the ESR1 gene and CA repeat in the THRA gene.

2. Subjects and methods

2.1. Subjects and DNA isolation

Genomic DNA was extracted from blood samples of 151 healthy individuals (74 women and 77 men, with mean age of 37 ± 19.8 years) and 151 CAD patients by a standard phenol–chloroform method [28]. All subjects were from southern Tunisia (Sfax region).

2.2. Patients' profile and clinical data

We recruited between 2007 and 2008, 151 unrelated coronary patients (95 women, 56 men, with mean age of 64 years), who had symptomatic CAD: acute coronary syndrome or stable angina, hospitalized at Cardiology Service of the Hedi Chaker University Hospital of Sfax, Tunisia. Acute coronary syndrome was diagnosed if at least one of the following criteria was met: unstable angina (Electrocardiogram changes without evidence of myocardial necrosis and clinical symptoms), acute myocardial infarction (positive markers of myocardial necrosis) including ST-segment elevation myocardial infarction.

These patients underwent coronary angiography following a myocardial infarction, angina, chest pain or heart failure. After angiography, the group of patients ($n = 64$) with a stenosis more than 50% on at least one major coronary artery was divided into 3 subgroups according to the number of affected coronary arteries. The absence of significant coronary stenosis (⩽50%) was designated (V0, $n = 66$).

After a detailed explanation of the purpose of the study, a written informed consent was obtained from all patients. The study protocol was approved by the local committee of Medical Ethics (Hedi Chaker Hospital Ethics Committee, Sfax). The work has been carried out in accordance with The Code of Ethics of the World medical Association (Declaration of Helsinki) for experiments in humans.

2.3. Biochemical analysis

Serum concentrations of glucose, triglycerides (TG), total cholesterol and urea were measured by the standard methods used in the clinical laboratory of the hospital.

Table 1 Frequency of R497K, I655V and T594T in the Tunisian population.

	Gene	Controls Count (%)	CAD patients Count (%)	*Chi* square (*p*-value)
rs11543848 (R497K)	*EGFR*			
Genotype				
AA		12 (7.95)	14 (9.27)	1.64 (0.44)
AG		47 (31.12)	56 (37.09)	
GG		92 (60.93)	81 (53.64)	
Allele				
A		71 (23.51)	84 (27.81)	1.47 (0.22)
G		231 (76.49)	218 (72.18)	
rs1801200 (I655V)	*HER2*			
Genotype				
AA		84 (83.17)	123 (82)	0.06 (0.8)
AG		17 (16.83)	27 (18)	
GG		0 (0)	0 (0)	
Allele				
A		185 (91.6)	273 (91)	9.13 (0.82)
G		17 (8.4)	27 (9)	
rs2228440 (T594T)	*ESR 1*			
Genotype				
AA		14 (9.27)	3 (3.3)	4.12 (0.12)
AG		44 (29.14)	34 (37.36)	
GG		93 (61.59)	54 (59.34)	
Allele				
A		72 (23.84)	40 (21.98)	0.22 (0.63)
G		230 (76.16)	142 (78.02)	

EGFR: epidermal growth factor receptor gene, HER2: Human Epidermal growth factor Receptor 2 gene, ESR1: estrogen receptor α gene, I: isoleucine, V: valine, R: arginine, K: lysine, T: threonine, CAD: coronary artery diseases.

2.4. Genotyping

The single nucleotide polymorphisms: rs11543848 (R497K) of the EGFR gene, rs1801200 (I655V) of the HER2 gene and rs2228440 (T594T) of the ESR1 gene (Table 2) were typed by polymerase chain reaction (PCR) amplification using the conditions described by Zhang et al. [29], Kalemi et al. [30] and Akisik and Dalay [31], respectively, followed by restriction enzyme digestion. The AC repeat of the THRA gene (accession number NG_008493) was typed by Applied Biosystems Automated Genetic Analysers (ABI3100-Avant) with Genscan software (V3.5). PCR products of the reference THRA sequence were 270 bp in length and contain 15 AC repeats (using the conditions given by Shearman et al. [32]). All PCR reactions were performed by using a GenAmp PCR system 9600 thermocycler (Perkin–Elmer).

2.5. Statistical analysis

The genotypic frequencies were calculated by simple counting using Microsoft-Excel. The estimation of allele frequency and exact test for Hardy–Weinberg equilibrium was performed using the Genetic Data Analyses program (version 1.1) [33]. Genotypic and allelic frequencies were compared between controls and patients using standard chi square test at a 5% level of significance. For comparing microsatellite allelic frequencies between controls and patients we also used the Clump program [34]. This program proposes different tests and provides *p*-values that are corrected for multiple testing. Odds ratio for the case–control association study and their 95% confidence intervals were estimated using programs from Linkage Utility Package (http://linkage.rockefeller.edu). In patients with CAD, correlation between the genotypes and clinicopathological characteristics was carried out with the SPSS program (version 21.0).

3. Results

3.1. Association between polymorphisms and CAD

3.1.1. Association analysis of the I655V, R497K and T594T polymorphisms

Allelic and genotypic frequencies of the HER2 I655V, EGFR R497K and ESR1 T594T polymorphisms in CAD patients and healthy individuals are given in Table 1. No significant deviation from Hardy–Weinberg equilibrium was found for any of the SNPs studied ($p = 0.137$, $p = 0.086$ and $p = 0.2$ for the R497K, I655V and T594T polymorphisms, respectively). The allelic and genotypic frequencies of the 3 SNPs were similar in the patient and control groups, and the difference between the frequencies was not statistically significant (Table 1).

When the three polymorphisms are tested together by binary logistic regression, no association was found with any of them.

3.2. Association analysis of the THRA repeat polymorphism

THRA repeat was successfully genotyped in 150 healthy unrelated individuals and 147 individuals with CAD. The level of heterozygosity was estimated as 81.9%. Hardy–Weinberg

Table 2 *THRA* microsatellite and cardiovascular disease risk in the Tunisian population.

	Controls Count (%)	Patients Count (%)	Chi square (*p*-value)	OR (95% CI)
Alleles				
S (⩽20)	215 (71.67)	189 (64.3)	3.712 (0.053)	0.71 (0.5–1.01)
L (>20)	85 (28.33)	105 (35.7)		
Genotypes				
SS	78 (52)	65 (44.22)	1.8 (0.179)	0.73 (0.49–1.16)
SL	59 (39.3)	59 (40.14)	0.019 (0.95)	1.03 (0.65–1.65)
LL	13 (8.7)	23 (15.64)	3.39 (0.065)	1.95 (0.95–4.02)

THRA: thyroid hormone receptor α gene, OR: odd ratio, S: short alleles (⩽20 repeats), L: long allele (>20 repeats).

equilibrium was satisfied (exact $p = 0.06$). Forty-five genotypes (14 alleles) were found in the Tunisian control group against 42 genotypes (13 alleles) in patients. The most prevalent genotype was 18/20 (15.3% and 16.3% in controls and CAD patients, respectively) whereas most of the genotypes had a frequency less than 5%. The allelic frequencies were very similar between patients and controls, and no significant difference was found when comparing all alleles by Clump ($p = 0.33$) or each individual allele separately. Also, if we define two classes of alleles, S (short) for alleles with ⩽20 repeats and L (long) for >20, no significant association was found ($p = 0.053$) (Table 2).

3.3. Association of polymorphisms with clinical and biochemical parameters

The analysis of possible association of the genotype polymorphisms with the clinical and biochemical parameters of CAD showed five significant associations (Table 3). The first is between the SNP R497K of the EGFR gene and the glycemia level ($p = 0.008$). A high level of glycemia is correlated with the presence of AG genotype. The second is between the THRA microsatellite and the TG serum level ($p = 0.0024$). Subjects with LL genotypes have the lowest serum levels of TG. The others, are between the SNP T594T of the ESR1 gene and the smoking habit ($p = 0.002$) as well as urea ($p = 0.037$) and TG ($p = 0.019$) levels. The genotypes AG and GG were more prevalent among nonsmokers and were associated with high TG and urea levels, respectively.

Also, multivariate analysis was performed using the clinical or biochemical parameter as dependent variable and the markers' genotypes as explanatory variables adjusted for other clinical and biochemical variables. But, no significant association was found for the four polymorphisms ($p > 0.05$).

4. Discussion

In the present study, we examined the possibility of association between CAD and four polymorphisms in a southern Tunisian sample: R497K polymorphism of the EGFR gene, I655V polymorphism of the HER2 gene, T594T polymorphism of the ESR1 gene and the microsatellite D17S2189 of the THRA gene with CAD. Distribution of allele or genotype frequencies of the four polymorphisms in our case-control sample does not reveal any significant association, and this finding persisted after adjusting for several potential confounding factors.

However, analyzing the relationship between the 4 polymorphisms and the clinical and biochemical parameters of our cohort, a significant association was found between the SNP R497K and the glycemia level. A high level of glycemia was correlated with the presence of AG genotype. The role of this polymorphic site in CAD was established in many studies where it was associated with the risk of acute coronary syndrome [7] and dilated cardiomyopathy [8] in a Chinese population. These authors suggested that genetic polymorphism of EGFR (Arginine → Lysine) might be clinically important in the development and progression of these diseases but the exact mechanism by which the Lys allele may act is unclear. In 1993, a variant EGFR of an arginine to lysine substitution at codon 497 was identified [35]. Wild-type EGFR (Arg allele) differs from mutant EGFR (Lys allele) with respect to epithelial proliferation following the administration of EGF and TGF-α in rodents [36]. Thus, it was suggested that mutations which influence the function or expression of EGFR (such as attenuating its ligand binding as well as subsequent activation of its downstream effectors) might predispose to development of some diseases and phenotypes.

Also, a significant association was observed between the THRA microsatellite and the TG serum level. Subjects with LL genotypes possess the lowest serum level of TG. This result suggest that long allele of this microsatellite may have a protective effect against TG increases. To our knowledge, this is the first time that this polymorphic site was investigated for an association study with CAD. However, the relationship between this genetic variant and thyroid cancer risk was investigated in many studies [37–39] and it was suggested in a study performed on a Japanese population, that less aggressive thyroid cancer is correlated with increased THRA expression and an expanded THRA microsatellite [37]. These authors have suggested also that the size of this microsatellite can have an influence on the splicing phenomenon and on the expression of THRA isoforms based on the fact that the THRA repeat polymorphism is located in exon 9, near a splice junction.

Likewise, our results showed a significant correlation between the SNP T594T of the ESR1 gene and the smoking habit as well as urea and TG levels. The genotypes AG and GG were more prevalent among nonsmokers and were associated with high TG and urea levels, respectively. This result suggests the importance of ER in CAD via its association with some classical risk factors including smoking, high TG and urea levels. The effects of estrogen on the cardiovascular system, mediated mainly by ERα, have been well defined and specific polymorphisms in the ESR1 gene have been associated

Table 3 Association results of polymorphisms genotypes with clinical and biochemical parameters.

Characteristic	Number (Genotype frequency%)											
	R497K (*EGFR*)			I655V (*HER2*)			T594T (*ESR1*)			D17S2189 (*THRA*)		
	AA	AG	GG	AA	AG	GG	AA	AG	GG	SS	SL	LL
Clinical and anthropometric parameters												
Sex												
Female	9 (9.6)	32 (34)	53 (56.4)	74 (79.6)	19 (20.4)	0 (0)	1 (2)	23 (46)	26 (52)	38 (40.4)	44 (46.8)	12 (12.8)
Male	4 (7.1)	24 (42.8)	28 (50)	48 (87.3)	7 (12.7)	0 (0)	2 (5.1)	9 (23.07)	28 (71.8)	26 (49.05)	15 (28.3)	12 (22.64)
p-value[b]	0.566				0.27			0.06			0.062	
Age (years)	63.3 ± 2.57	61.56 ± 1.75	65.26 ± 1.29	64.51 ± 0.93	62.35 ± 2.99	0	67.33 ± 5.48	63.77 ± 1.85	66.81 ± 1.21	63.19 ± 1.53	63.12	67.25 ± 1.96
p-value[a]		0.58	0.504		0.495			0.591	0.934		0.978	0.109
Smoking habit												
Smoker	1 (3.44)	13 (44.83)	15 (51.72)	23 (79.3)	6 (20.7)	0 (0)	2 (8.69)	2 (8.69)	19 (82.6)	16 (57.14)	8 (28.57)	4 (14.28)
Not smoker	12 (11.21)	43 (40.18)	64 (59.81)	97 (82.9)	20 (17.1)	0 (0)	1 (1.53)	29 (44.61)	35 (53.84)	47 (40.51)	49 (42.24)	20 (17.24)
p-value[b]	0.525				0.6			**0.002**			0.293	
Diabete mellitus												
Diabetic	4 (6.77)	25 (42.3)	30 (50.84)	46 (80.7)	11 (19.3)	0 (0)	2 (4.25)	18 (38.3)	27 (57.44)	27 (48.21)	19 (33.93)	10 (17.86)
Not diabetic	9 (10.23)	31 (35.23)	48 (54.54)	73 (83)	15 (17)	0 (0)	1 (2.43)	13 (31.7)	27 (65.85)	36 (41.38)	37 (42.53)	14 (16.09)
p-value[b]	0.609				0.731			0.679			0.614	
Hypertension												
Hypertensive	7 (8.23)	37 (43.53)	41 (48.23)	70 (84.3)	13 (15.7)	0 (0)	2 (3.92)	20 (39.21)	29 (56.86)	31 (38.27)	33 (40.74)	17 (20.99)
Not hypertensive	1 (14.28)	3 (42.86)	4 (57.14)	8 (100)	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)	6 (75)	2 (25)	0 (0)
p-value[b]	0.748				0.596			1			0.156	
DBP (mmHg)	139.09 ± 5.79	143.9 ± 3.98	149.48 ± 3.38	140.56 ± 2.79	147.05 ± 7.01	0	150 ± 15.27	142.63 ± 5.18	146.1 ± 3.65	151.76 ± 3.68	142.1 ± 4	148.26 ± 4.97
p-value		0.501	0.139		0.396			0.685	0.825		0.079	0.574
SBP (mmHg)	80.9 ± 3.92	81.11 ± 2.5	81.11 ± 1.93	87.1 ± 2.32	87.03 ± 3.98	0	76.66 ± 12	76.89 ± 2.43	81.6 ± 2.65	83.83 ± 2.25	78.9 ± 2.34	81.95 ± 2.96
p-value[a]		0.966	0.962		0.989			0.987	0.724		0.133	0.616
Dyslipidemia												
Positive	7 (16.28)	14 (32.56)	22 (51.16)	34 (82.9)	7 (17.1)	0 (0)	2 (5.88)	16 (47.06)	16 (47.06)	20 (48.78)	15 (36.58)	6 (14.63)
Negative	6 (5.77)	42 (40.38)	56 (53.84)	85 (81.7)	19 (18.3)	0 (0)	1 (1.85)	15 (17.78)	38 (70.37)	43 (42.57)	41 (40.19)	18 (17.64)
p-value[b]	0.122				1			0.067			0.803	
CAD severity*												
v0	5 (7.57)	23 (34.84)	38 (57.57)	54 (80.6)	13 (19.4)	0 (0)	1 (4.34)	8 (34.8)	14 (60.86)	25 (37.31)	30 (44.77)	12 (17.91)

(*continued on next page*)

Table 3 (*continued*)

Characteristic	Number (Genotype frequency%)											
	R497K (*EGFR*)			I655V (*HER2*)			T594T (*ESR1*)			D17S2189 (*THRA*)		
	AA	AG	GG	AA	AG	GG	AA	AG	GG	SS	SL	LL
v1	5 (11.11)	17 (37.78)	23 (51.11)	38 (88.4)	5 (11.6)	0 (0)	1 (2.63)	12 (31.58)	25 (65.8)	23 (56.1)	11 (26.83)	7 (17.07)
v2	2 (25)	4 (50)	2 (25)	6 (75)	2 (25)	0 (0)	0 (0)	4 (50)	4 (50)	3 (42.85)	3 (42.85)	1 (14.28)
v3	1 (10)	4 (40)	6 (60)	9 (81.8)	2 (18.2)	0 (0)	1 (11.11)	1 (11.11)	7 (77.77)	5 (45.45)	5 (45.45)	1 (9.09)
p-value[b]	0.566				0.626			0.539			0.555	
Biochemical parameters												
Fasting glucose (μmol/l)	5.83 ± 0.81	9.05 ± 0.76	12 ± 4.24	10.82 ± 2.32	6.52 ± 0.44	0	11.45 ± 4.55	8.51 ± 1.09	13.98 ± 5.41	8.4 ± 0.63	7.72 ± 0.62	7.82 ± 1.09
p-value[a]		**0.008**	0.16		0.073			0.634	0.733		0.447	0.652
Urea (μmol/l)	9.31 ± 2.69	8.47 ± 1.05	7.04 ± 0.49	7.79 ± 0.47	9.28 ± 1.87	0	5.72 ± 0.77	10.37 ± 1.89	7.02 ± 0.52	8.35 ± 1.03	7.82 ± 0.71	6.87 ± 0.94
p-value[a]		0.778	0.436		0.451			**0.037**	0.293		0.525	0.3
Triglyceride (mmol/l)	2.02 ± 0.19	1.67 ± 0.14	2.06 ± 0.26	1.9 ± 0.14	1.83 ± 0.23	0	1.28 ± 0.03	1.61 ± 0.17	1.98 ± 0.27	1.76 ± 0.14	2.18 ± 0.29	1.3 ± 0.12
p-value[a]		0.175	0.907		0.802			0.09	**0.019**		0.218	**0.024**
Total cholesterol (mmol/l)	4.85 ± 0.45	13.48 ± 8.42	8.01 ± 2.23	9.72 ± 3.29	4.42 ± 0.84	0	5.11 ± 0.36	4.98 ± 0.46	8.17 ± 2.48	5.99 ± 0.58	15.02 ± 10	4.99 ± 0.676
p-value[a]		0.3219	0.175		0.124			0.835	0.235		0.381	0.278

DBP: diastolic blood pressure, SBP: systolic blood pressure, EGFR: epidermal growth factor receptor gene, HER2: human epidermal growth factor receptor 2 gene, ESR1: estrogen receptor α gene, THRA: thyroid hormone receptor α gene, I: isoleucine, V: valine, R: arginine, K: lysine, T: threonine.

Significant associations are in bold.

[*] Based on number of affected coronary arteries: stenosis $< 50\%$ of one (V0), $\geqslant 50\%$ of one (V1), two (V2), or three (V3) major coronary arteries.

[a] *p*-value of student's *t*-test of mean comparison with AA genotype as a reference group.

[b] *p*-value of Fisher's exact test.

with several coronary heart diseases including CAD, hypertension and stroke in studies covering different populations [24,40,41]. Although that the SNP T594T is synonymous and yields no change in protein sequence, its importance has been highlighted in many investigations where it has been suggested that the mechanism of action may involve alternative gene regulation and transcript processing [39,42].

Regarding the SNP I655V of the HER 2 gene and despite the absence of significant association in our study, the importance of this polymorphism has been highlighted in many studies and according to the secondary structure prediction of the transmembrane domain, it has been suggested that the presence of the I residue at position 655 might destabilize the formation of active HER2 dimers and reduce phosphotyrosine kinase activity even in the presence of receptor overexpression [43]. More recently, Pinto et al. [44] have suggested that the genotype GG confers high heterodimerization capacities to the receptor that can activate more powerfully the intracellular signaling pathways of HER2 such as MAPK and PI3P/AKT. The involvement of the HER2 receptor in CAD has been revealed in many studies. In a recent study, the authors showed an association between a decreased expression of ErbB2/HER2 and the release of troponins and the need for inotropic therapy in patients with acute heart failure and they conclude that the molecular function of the HER2 receptor may be essential for the prognosis and targeted therapy of heart diseases [45]. Also, it has been shown that targeting the HER2 receptor in the anticancer therapy may lead to the deterioration of left ventricular cardiac function [11]. Later, the SNP I655V has been associated with cardiac toxicity in breast cancer patients treated with Trastuzumab [46].

5. Conclusion

Our results suggest the absence of any significant association between the four genetic variants analyzed and CAD risk as well as disease severity. However, these polymorphic sites may be involved in such diseases indirectly through the intermediary of their association with some classic risk factors such as smoking habit, glycemia, urea and TG levels. These results are encouraging to conduct advanced studies evaluating with precision the role of these genetic variants and their respective genes in CAD.

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