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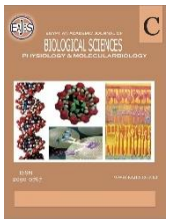

The 1059G>C Polymorphism in C-Reactive Protein Gene and Its Association with Susceptibility to Type 2 Diabetes in the Moroccan Population

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ABSTRACT

Human C-reactive protein (CRP) is an acute phase reactant involved in chronic and acute inflammation, which plays an important role in developing many diseases, such as type 2 diabetes (T2D). This study aimed to evaluate the association between CRP 1059G>C Polymorphism and predisposition to T2D in patients from a population of Morocco. We analyzed data from 212 patients with T2D and 158 controls. After the DNA is extracted from the blood samples, Polymerase Chain Reaction (PCR) and agarose gel electrophoresis are performed to determine the CRP gene's 1059G>C polymorphism. In the comparison between the control and patient groups, there was a significant difference in both genotype and allele frequencies ($P < 0.0001$ and $P < 0.0001$, respectively). The prevalence of GG and GC genotypes in diabetic patients was 96.7% and 3.3%, respectively, while in controls, it was 81.6% and 18.4%, respectively. The heterozygote GC was associated with a higher risk of T2D compared to the GG genotype (OR = 0.15, 95%CI = 0.06–0.35, $P < 0.001$). Regarding the allele frequencies, in the diabetic group, the G and C alleles were found at 98.3% and 1.7%, respectively, while in controls, they were present at frequencies of 90.8% and 9.2%, respectively. The CRP C allele was associated with a 0.16-fold decreased risk of T2D compared to the G allele (OR = 0.16, 95%CI = 0.07–0.38, $P < 0.001$). These results indicate a significant association between the CRP 1059G>C polymorphism and T2D in the Moroccan population.

INTRODUCTION

In its entirety, Type 2 diabetes (T2D) presents a significant global health issue (Wild et *al*., 2004), wherein genetic modifications play a pivotal role in determining why certain diabetic patients experience complications, in contrast, others remain unaffected (Marre *et al*., 2000).

A substantial body of evidence underscores the importance of inflammation in developing diabetic complications, focusing on the exacerbation of atherosclerosis and complications (Schulze *et al*., 2004). According to the International Diabetes Federation, the current number of individuals with diabetes worldwide is estimated at around 537 million, and this figure is projected to rise to 783 million by the year 2045 (IDF, 2021).

T2D entails significant morbidity and mortality, mainly due to its associated complications, such as renal failure, amputations, cardiovascular disease (CVD), and cerebrovascular events (ADA, 2013).

The liver synthesizes C-reactive protein (CRP) in response to inflammatory processes. CRP acts as an acute phase reactant in acute and chronic human inflammation (Kushner, 1982). The regulation of CRP expression involves trans-acting cytokines like tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-1 (IL-1), which are produced by hepatocytes (Li & Fang, 2004; Visser *et al*., 1999).

Chronic inflammation has been linked to various disorders, such as CVD, atherosclerosis, and T2D (Libby et *al*., 2002; Mazzone et al., 2008). Consequently, blood CRP levels have become a dependable predictor of inflammation and overall patient health (Myburgh *et al*., 2020). Elevated CRP levels have been associated with obesity, atherosclerosis, insulin resistance, metabolic syndrome (MetS), and diabetes (Gelaye *et al*., 2010; Lai *et al*., 2010; Momiyama *et al*., 2010; Peper *et al*., 2022; Rizzello *et al*., 2007; Shankar & Li, 2008).

Research has shown that a significant proportion, nearly 40%, of the variation in plasma CRP protein levels can be attributed to genetic factors (Kaur *et al*., 2013).

The human CRP gene has two exons that are separated by an intron, and is located on chromosome 1q21–q23. A signal peptide and the first two amino acids of the mature CRP protein are both encoded by the first exon. On the other hand, the second exon encodes the protein's final 204 amino acids. (Hage & Szalai, 2007).

Studies have indicated that a synonymous polymorphism, 1059G>C (CTG>CTC, Leu>Leu at codon 184), may impact CRP protein levels and contribute to the progression of T2D (Lange *et al*., 2006; Pašalić *et al*., 2009). Therefore, the current investigation aims to evaluate the correlation between the 1059G>C polymorphism and individuals diagnosed with T2D in the Moroccan population.

MATERIALS AND METHODS

1. Study Subjects:

Data from the study was carried out in consultant patients in the diagnostic center of Rabat, Morocco; informed oral consent was obtained for each patient. Three hundred seventy (370) subjects from both genders were included. Anthropometric measurements, measurement of blood pressure and the dosage of biochemical parameters such as Age, waist (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), Glycemia, triglyceride (TG), cholesterol (CHO), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were taken from each participant.

The diagnosis of diabetes in this study adhered to the guidelines set forth by the World Health Organization (WHO). According to these criteria, individuals were classified as having diabetes if their fasting glucose level exceeded 126 mg/dl (7.0 mmol/l). Conversely, controls were classified as non-diabetic based on the same criteria.

2. Genotyping:

DNA was obtained using the high ionic protein recharging technique and used as the amplification template for polymerase chain reaction (PCR) (Montgomery & Sise, 2012). The method involves centrifuging the blood sample, collecting the leukocyte cloud, and treating the cell pellet with a K proteinase to digest cellular proteins. A lysis solution comprising EDTA-Na2 (10mM), SDS (0.2%), Tris-HCl (10mM, pH 7.5), and NaCl (50mM) is added to lyse the white blood cells. The remaining components are subsequently precipitated using the ionic force of NaCl (6M). Finally, a cold (95% concentration) ethanol solution is added to precipitate the genomic DNA.

The CRP 1059G>C polymorphism was evaluated through PCR amplification, employing specific primers with the following sequences: allele G specific reverse (5′A-TGGTGTTAATCTCATCTG GTGGC3′) allele C specific reverse (5′ATGGTGTTAA-

TCTCATCTGGTGGG3′), and a constant forward (5′CATTTGTACAAGCTGG-GAGT3′).The amplification process was conducted using a thermal cycler. The PCR conditions involved an initial denaturation step at 95 °C for 5 minutes, followed by a touchdown PCR protocol. This protocol included denaturation at 94 °C for 45 seconds and annealing at temperatures ranging from 63 °C for 50 seconds. Extension occurred at 70 °C for 50 seconds during each cycle, with a final extension step at 73 °C for 15 minutes.

The CRP 1059G>C genotypes were identified based on the presence or absence of a 237 bp PCR amplicon. Gel electrophoresis on a 2% agarose gel stained with ethidium bromide (BT) was employed to visualize the PCR products. A 100 bp ladder was used as a molecular weight marker to determine the fragment size accurately. These experimental techniques facilitated accurate genotyping of the study population's CRP 1059G>C polymorphism.

3. Statistical Analysis:

The statistical analyses conducted in this research utilized the Statistical Analysis System (SAS) software.

Descriptive statistics such as mean and standard deviation (SD) were reported for continuous data, and Student t-tests were employed to compare continuous variables between different groups. A significance level of $P<0.05$ was adopted to address potential multiple comparisons.The genotype distributions were examined for adherence to the Hardy-Weinberg Equilibrium (HWE) using chi-square analysis. Additionally, chi-square tests (χ^2) were employed to assess genotype and allele frequencies between the cases and controls.

To estimate the strength of associations, odds ratios (ORs) were calculated along with their corresponding 95% confidence intervals (CIs). These analyses were essential for evaluating the relationships between variables and determining potential associations in the study population.

RESULTS

Metabolic and anthropometric characteristics of the study population are summarized in Table 1. The average values of Glycemia, SBP, DBP, WC, CHO, and TG were significantly higher ($P < 0.0001$), LDL is moderately significant ($P < 0.0063$), and HDL is not significant ($P < 0.0662$), in patients with diabetes than those without diabetes.

Table 1. Anthropometric and metabolic characteristics in the study population.

Parameters	Controls (mean±SD)	Diabetics (mean±SD)	P value
Glycemia (g/l)	0.88 ± 0.09	1.90 ± 0.60	< 0.0001 (***)
WC (cm)	82.11 ± 6.71	91.14 ± 10.81	< 0.0001 (***)
SBP (mmHg)	128.08 ± 11.21	141.72 ± 18.59	< 0.0001 (***)
DBP (mmHg)	72.32 ± 6.08	78.45 ± 11.91	< 0.0001 (***)
TG (g/l)	0.97 ± 0.54	1.50 ± 0.86	< 0.0001 (***)
CHO (g/l)	1.81 ± 0.40	1.98 ± 0.41	< 0.0001 (***)
LDL (g/l)	1.04± 0.36	1.15 ± 0.37	< 0.0063 (**)
HDL (g/l)	0.58 ± 0.20	0.54 ± 0.23	< 0.0662 (N.S)

Note: ***P<0.001; **P<0.01; *P<0.05. T2D. type 2 diabetes; TC. total cholesterol; TG. triglyceride; HDL. high-density lipoprotein cholesterol; LDL. low-density lipoprotein cholesterol; SBP. systolic blood pressure; DBP. diastolic blood pressure.

Upon analyzing the genotype frequencies for the CRP 1059G>C polymorphism, a deviation from HWE was observed in both T2D patients and controls. Moreover, the cases and controls showed a notable disparity in genotype distribution. ($P < 0.0001$) (Table 2).

Specifically, the percentage of heterozygous GC individuals was notably lower (3.3%) among diabetic patients

compared to controls (18.4%). Conversely, a higher percentage of homozygous GG individuals was observed in the patient group (96.7%) compared to the control group (81.6%).

In addition, the allele frequency analysis revealed a lower prevalence of the C allele (1.7%) in T2D patients compared to controls (9.2%).

Table 2. Distribution of the genotypes and alleles frequencies in the study population.

CRP 1059 G>C	T2D (n=212)	Control (n=158)	OR (95% CI)	P-value
GG	205 (96.7%)	129 (81.6%)	1.00 **(Reference)**	
GC	7 (3.3%)	29 (18.4%)	0.15 (0.06 - 0.35)	**P < 0.0001**
CC	0 (0%)	0 (0%)	0.63 (0.01 - 31.95)	P = 0.8177
			P of trend < 0.0001	
GC+CC	7	29	6.58 (2.80 - 15.47)	P < 0.0001
G	417 (98.3%)	287 (90.8%)	1.00 (Reference)	
C	7 (1.7%)	29 (9.2%)	0.16 (0.07-0.38)	**P < 0.0001**
Note: ***P<0.001; **P<0.01; *P<0.05 T2D. type 2 diabetes; OR. odd ratio; CI. confidence interval				

The calculated OR for the GC genotype was 0.15, indicating a statistically significant negative association with diabetes. This finding suggests that individuals with the GC genotype have a lower likelihood of developing diabetes compared to those with the GG genotype.

DISCUSSION

Identifying genetic risk factors may make it easier to forecast the possibility that a disease will occur and adopt personalized treatments. Even while more than 80 susceptibility loci have been found in previous genome-wide association studies (GWAS) for diabetes, these results only partially explain the heritability of the disease (Fuchsberger *et al*., 2016). Consequently, genes responsible for encoding proteins associated with inflammatory pathways emerge as significant contenders in T2D. Genetic variations in these genes influence an individual's susceptibility to disease development (Aul *et al*., 2002). This is the first study analyzing the association of CRP 1059G>C polymorphism and T2D in the Moroccan population. In the current investigation, we found a significant difference in the genotype distribution of CRP between T2D cases and healthy controls. We have observed that the dominant GG genotype (96.7% in diabetic patients compared to 81.6% for controls) and G-allele (98.3% in diabetic patients compared to 90.8% for controls) of the CRP are linked to an increased risk of T2D in the Moroccan population.

There have been limited investigations on the connection of CRP 1059G>C polymorphism with T2D in other international populations. Furthermore, the general association studies have shown contradictory results (Jebur *et al*., 2019; Lange *et al*., 2006; Yazici *et al*., 2010). Similar frequencies of the G-allele have been noted in investigations on people worldwide (Balistreri *et al*., 2006; Grammer *et al*., 2009; Kaur *et al*., 2013; Pašalić *et al*., 2009).

Our findings are consistent with research on a North-West Indian community that found the GG genotype to be a risk factor for T2D susceptibility (Kaur *et al*., 2013). Conversely, an increased prevalence of mutant alleles was identified in individuals diagnosed with T2D compared to healthy individuals. Additionally, an independent relationship was observed between the mutant CC genotype and the GC heterozygous genotype of the CRP gene, indicating an elevated risk of developing T2D (Jebur *et al*., 2019).

Previous research conducted by other investigators did not provide evidence

supporting a relationship between the investigated polymorphism and T2D. In a study involving Turkish T2D patients, they observed higher CRP levels in the patient group compared to controls. However, their findings did not demonstrate any association between the 1059G>C polymorphism and CRP levels or T2D (Yazici *et al*., 2010).

In the context of an association study investigating the relationship between CRP levels and the 1059G>C polymorphism with MetS, individuals carrying the C allele of the CRP 1059G>C polymorphism exhibited a higher risk of developing MetS. The MetS was defined as clustering three or more vascular risk factors, including high fasting glucose. Furthermore, the study identified the CRP gene and CRP levels as independent risk factors for MetS (Abd El-Aziz & Mohamed, 2013).

CRP 1059G>C polymorphism is a specific genetic variation named synonymous polymorphism; it has been linked to alterations in CRP protein levels and is associated with the development and progression of both coronary artery disease (CAD) and T2D (Jebur *et al*., 2019).

The CRP levels can be influenced by various variables, including smoking, obesity, and hereditary factors (Van Leeuwen & Van Rijswijk, 1994). it is noteworthy to emphasize that adipose tissue, particularly in the abdominal region, plays a vital role in hormone synthesis, notably the production of leptin, and also contributes to the generation of cytokines, such as IL-6 and TNF (Visser *et al*., 1999). Leptin, particularly, has proinflammatory qualities because it stimulates adipocytes to produce cytokines (Ikonomova, 2004). Chronic adipose tissue inflammation is vital in developing insulin resistance associated with obesity (Xu et *al*., 2003). In insulin resistance, hepatocytes change their protein synthesis toward producing acute-phase proteins (Festa *et al*., 2000). As a result, CRP may act as a connection between obesity, insulin resistance, and CAD (Groop, 2000).

Considering the 1059G>C polymorphism as a silent mutation within exon 2 of the CRP gene (Cao & Hegele, 2000), its impact on serum CRP concentration could be attributed to its linkage disequilibrium with nearby genetic polymorphisms, particularly those in the promoter region (Kovacs *et al*., 2005). The 1059G>C polymorphism is another potential mechanism that may have an impact on the stability of CRP mRNA., consequently leading to alterations in the serum CRP concentration. Moreover, the NHLBI Family Heart Study reported a heritability of CRP to be around 35-40% (Pankow *et al*., 2001), implying that acquired factors hold a similar level of importance as genetic factors in determining serum CRP concentration.

In conclusion, the study focused on the CRP 1059G>C polymorphism and its association with T2D in the Moroccan population. The findings revealed a significant difference in the genotype distribution of CRP between T2D cases and healthy controls, with the GG genotype and G-allele of the CRP gene being linked to an increased risk of T2D.

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ARABIC SUMMERY

تعدد الأشكال 1059G>C في مورثة البروتين سي التفاعلي (CRP) وارتباطه بالقابلية للإصابة بمرض السكري من النوع 2 لدى السكان المغاربة

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يعد بروتين سي التفاعلي البشري (CRP) أحد المواد المتفاعلة في الطور الحاد المشاركة في الالتهابات المزمنة والحادة، والذي يلعب دورا مهما في تطور العديد من الأمراض، مثل مرض السكري من النوع 2 (T2D). تهدف هذه الدارسة إلى تقييم العلاقة بين تعدد الأشكال CRP 1059G>C والقابلية للإصابة بمرض السكري لدى المرضى من سكان المغرب. قمنا بتحليل البيانات المحصل عليها من 212 مريضا يعانون من T2Dو158 من الأشخاص الشواهد. بعد استخراج الحمض النووي من عينات الدم، يتم إجراء تفاعل البوليميراز المتسلسل للحمض النووي (PCR) متبوعا بالهجرة الكهربائية في هلام الاغاروز لتحديد تعدد الأشكال الخاص بالمورثة CRP 1059G>C. من خلال المقارنة بين مجموعة الشواهد بمجموعة المرضى، كان هناك اختلاف كبير في كل من النمط الوراثي وترددات الحليل ($p < 0.0001$ و $p < 0.0001$، على التوالي). بلغ معدل انتشار الأنماط الجينية GG وGC في مرضى السكري 96.7% و3.3% على التوالي، بينما بلغ في مجموعة الشواهد 81.6% و18.4%، على التوالي. ارتبط متغاير الزيغوت GC بارتفاع خطر الإصابة ب T2D مقارنة بالنمط المتماثل الزيغوت GG (OR = 0.15، 95٪ CI = 0.06-0.35، $p<0.001$). فيما يتعلق بترددات الحليلات، تم العثور على الحليلين G وC بنسبة 98.3% و1.7% على التوالي، بالنسبة لمجموعة مرضى السكري، بينما كانت نسبة هذين الترددين هي 90.8% و9.2% على التوالي، بالنسبة لمجموعة الشواهد. من خلال تحليل النتائج المحصل عليها، يمكن القول بان الحليل C للمورثة CRP مرتبط بانخفاض خطر الإصابة ب T2D بمقدار 0.16 مقارنة بالحليلG (OR = 0.16, 95%CI = 0.07–0.38, P < 0.001). تشير هذه النتائج إلى وجود ارتباط كبير بين تعدد الأشكال CRP 1059G>C وT2D في السُّكان المغاربة. ومع ذلك، من الضروري إجراء دراسات أخرى داخل عينات أكبر، لتأكيد نتائج هذه الدراسة والتوصل إلى نتائج نهائية في هذا الموضوع.