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# The C-565T Polymorphism (rs2422493) of the ATP-binding Cassette Transporter A1 Gene Contributes to the Development and Severity of Coronary Artery Disease in an Iranian Population

Khalil Mahmoodi[1], Koorosh Kamali[2], Habib Ghaznavi[3] and Mohammad Soleiman Soltanpour[4]*

[1]Department of Cardiology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[2]Department of Public Health, School of Public Health, Zanjan University of Medical Sciences, Zanjan, Iran
[3]Health Promotion Research Centre, Department of Pharmacology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran
[4]Department of Medical Laboratory Sciences, School of Paramedical Sciences, Zanjan University of Medical Sciences, Zanjan, Iran

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**ABSTRACT**

***Objectives:*** ATP-binding cassette transporter A1 (ABCA1) plays a pivotal role in reverse cholesterol transport from peripheral tissues back to the liver. Abnormalities in ABCA1 function may lead to dyslipidemia and coronary artery disease (CAD). We investigated the role of C-565T (rs2422493) promoter polymorphism of ABCA1 gene in the development and severity of CAD in an Iranian subpopulation. ***Methods***: Our study population consisted of 110 angiographically-confirmed CAD patients and 110 matched controls. The severity of CAD was expressed based on the number of stenotic vessels. Genotyping of C-565T promoter polymorphism was performed using the polymerase chain reaction followed by restriction fragments length polymorphism analysis methods. Lipid profile was determined by routine colorimetric methods. ***Results:*** The distribution of ABCA1 C-565T genotypes ($p$ = 0.035) and alleles ($p$ = 0.017) was significantly different between the CAD and control groups. In univariate analysis (with genotype CC as reference), the TT genotype was significantly associated with an increased risk of CAD (odds ratio = 3.83; 95% confidence interval: 1.29–11.30, $p$ = 0.014), but the CT genotype was not ($p$ = 0.321). A multiple binary logistic regression analysis revealed that smoking, hypertension, triglyceride, cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and ABCA1 C-565T dominant genotype were significant and independent risk factors for CAD development ($p$ < 0.050). The ABCA1 C-565T polymorphism affected the severity of CAD in TT homozygote state ($p$ = 0.028). However, no significant correlation was seen between this common polymorphism and lipid profile in the study population ($p$ > 0.050). ***Conclusions:*** Our study indicated that ABCA1 C-565T polymorphism is a significant risk factor for development and severity of CAD in our population.

Coronary artery disease (CAD) remains one of the most important causes of morbidity and mortality in the Iranian population.[1] Several lines of evidence suggest that the interaction of both genetic and environmental risk factors are involved in the pathogenesis of CAD.[2] Dyslipidemia is a known risk factor for CAD occurrence that can be generated by acquired and genetic risk factors or by interactions of both.[3,4] Decreased high-density lipoprotein cholesterol (HDL-C) level has been reported as the most common lipid abnormality in patients with CAD.[5] HDL-C is an alpha lipoprotein particle that functions in reverse cholesterol transfer (RCT) from peripheral tissues back to hepatic tissue.[6] The initial step in the biogenesis of HDL-C is mediated by a protein known as ATP-binding cassette transporter A1 (ABCA1), which facilitates the efflux of cholesterol from peripheral tissues to lipid-poor apolipoprotein A-I, creating nascent high-

*Corresponding author: ✉soltanpourm@zums.ac.ir

density lipoprotein particles.[6,7] Reduced activity of ABCA1 may impair HDL-C formation and lead to decreased cholesterol efflux from peripheral tissues back to the liver.[8] Homozygous mutations of ABCA1 gene have been associated with Tangier disease, which is characterized by lack of HDL-C in plasma and an increased tendency to develop premature cardiovascular disease.[9] Also, several common polymorphisms have been identified in ABCA1 gene that may affect lipid metabolism and predispose carriers to CAD development.[10,11] The C-565T (rs2422493) promoter polymorphism of ABCA1 gene has been shown to cause decreased gene expression in some studies and has been proposed as a risk factor for development and severity of CAD.[12,13] The allele frequency of this polymorphism in the general Iranian population was reported as 19.5%.[14] Currently, no studies have investigated the role of this common polymorphism in Iranian CAD patients. We sought to determine the prevalence of C-565T promoter polymorphism of ABCA1 gene and the effect of this polymorphism on the lipid profile in an Iranian subpopulation of CAD patients.

## METHODS

Our study population comprised of 110 patients (56 male and 54 female) with angiographically-documented CAD and 110 ethnically and age-matched control subjects (55 male and 55 female). The diagnosis of CAD was confirmed by angiography performed by an expert cardiovascular specialist. The severity of CAD was determined based on the number of stenotic vessels showing more than 50% stenosis. Accordingly, patients were classified as single-, double-, and triple-vessel stenosis patients. CAD patients with luminal stenosis of 50% were included in the study. Patients with a previous history of myocardial infarction showing positive angiogram results were included in the study. Patients with luminal stenosis of < 50% or patients taking lipid-lowering drugs were excluded from the study. Also, patients with inflammatory disease, autoimmune disorders, infectious disease, overt organ failure, and cancer were excluded. The control subjects were selected randomly after careful inspection of a cardiovascular specialist. Control subjects were excluded from the study if they had a family history of CAD or suffered from concomitant diseases such as malignant diseases, organ failure, and febrile conditions. Information regarding the smoking habits, hypertension (as defined by systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg), diabetes (as defined by fasting blood glucose > 126 mg/dL), family history of heart disease, hyperlipidemia, and the presence of any acute or chronic disease was obtained from all participants. Written informed consent was obtained from all study subjects, and the study was approved by ethical committee of Zanjan University of Medical Sciences (Ethical code: ZUMS.REC.1394.268), Zanjan, Iran.

Genomic DNA was extracted from blood leukocytes using a commercially available DNA extraction kit (Viogene, Poland). The genotyping of ABCA1 C-565T polymorphism was conducted using the polymerase chain reaction (PCR) followed by restriction fragments length polymorphism analysis. The sequence of primers used for amplification of target DNA was: forward 5'-AAAGACTTCAAGGACCCAGCTT-3' and reverse 5'-CCTCACA TTCCGAAAGCATTA-3'. The amplification reaction was performed by a ready to use 2X master mix (Amplicon, Denmark) at an annealing temperature of 64 °C, which generated a 351 bp fragment of ABCA1 gene containing the C-565T polymorphic site. Restriction digestion was conducted on 8 µL PCR product using 5U of AciI (Fermentas, Germany) restriction enzyme in a total volume of 20 µL for 8 hours at 37 °C. The digested fragments were electrophoresed on 3% agarose gel and stained with Sybr Green dye. The presence of C allele generates two 278 bp and 73 bp fragments while the presence of T allele produces 148 bp, 130 bp, and 73 bp fragments.

Levels of biochemical markers including glucose, triglyceride (TG), total cholesterol (TC), HDL-C, and low-density lipoprotein cholesterol (LDL-C) were measured with calorimetric methods in a Mindray auto-analyzer (BS-200) using standard enzyme assay kits (Pars Azmoon Co, Tehran, Iran).

Data analysis was conducted using SPSS Statistics (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc). Numerical data were presented as mean±standard deviation (SD) and were compared using the Student's *t*-test. Categorical variables were compared using chi-square test or Fisher's exact tests. Multiple binary logistic regression analysis was used to detect the independent association of each risk factor with CAD. Chi-square test was used to check

**Table 1:** Baseline characteristics of patients with CAD and the control subjects.

| Variables | CAD n = 110 | Control n = 110 | *p*-value |
|---|---|---|---|
| Age, years | 59.1 ± 11.1 | 57.8 ± 15.5 | 0.526 |
| Sex, M/F | 56/54 | 55/55 | 0.997 |
| TG, mg/dL | 193.6 ± 82.5 | 163.2 ± 69.1 | 0.003 |
| TC, mg/dL | 204.5 ± 60.5 | 169.3 ± 46.5 | < 0.001 |
| HDL-C, mg/dL | 38.7 ± 9.1 | 46.3 ± 13.0 | < 0.001 |
| LDL-C, mg/dL | 101.4 ± 35.8 | 91.4 ± 32.7 | 0.031 |
| Hypertension | 26 (23.6) | 9 (8.1) | 0.002 |
| Diabetes | 28 (24.5) | 11 (10.0) | 0.004 |
| Smoking | 34 (30.9) | 13 (11.8) | 0.003 |
| C-565T genotypes (CC:CT:TT) | (47:48:15) | (60:45:5) | 0.035 |

*TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CAD: coronary artery disease; CC: wild-type; CT: heterozygote; TT: homozygote. n (%).*

**Table 3:** Results of multiple binary logistic regression analysis.

| Covariates | 95% CI | OR | *p*-value |
|---|---|---|---|
| **Age** | 0.97–1.03 | 1.01 | 0.406 |
| **Sex** | 0.47–2.00 | 0.97 | 0.951 |
| **Smoking** | 1.40–9.10 | 3.60 | 0.008 |
| **TG** | 1.00–1.01 | 1.00 | 0.006 |
| **TC** | 1.00–1.01 | 1.01 | < 0.001 |
| **HDL-C** | 0.90–0.96 | 0.93 | < 0.001 |
| **LDL-C** | 1.00–1.02 | 1.01 | 0.028 |
| **Diabetes** | 0.93–6.20 | 2.40 | 0.072 |
| **Hypertension** | 1.10–8.20 | 3.10 | 0.027 |
| **C-565T genotypes** | | | |
| CT+TT vs. CC | 1.10–4.00 | 2.10 | 0.032 |
| CC+CT vs. TT | 0.85–10.40 | 3.10 | 0.057* |

*TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CC: wild-type; CT: heterozygote; TT: homozygote, OR: odd ratio; CI: confidence interval. *Statistical power = 68.5%.*

for deviation of genotype distribution from the Hardy-Weinberg equilibrium in both groups. The association between CAD occurrence and the single nucleotide polymorphisms genotype and allelic frequencies were measured by the odds ratio (OR) with its confidence interval (CI). The statistical significance level was set at $p < 0.050$.

## RESULTS

The demographic, clinical, and laboratory data of CAD group and control group are presented in Table 1. The mean age of CAD patients and controls was 59.1±11.1 and 57.8±15.5 years, respectively. The two groups were similar in some variables including mean age and sex distribution. However, significant differences were observed regarding the plasma levels of TG ($p = 0.003$), TC ($p < 0.001$), HDL-C ($p < 0.001$), LDL-C ($p = 0.031$), diabetes ($p = 0.004$), hypertension ($p = 0.002$), and smoking habit ($p = 0.003$) between the groups [Table 1]. The genotype distribution of ABCA1 C-565T polymorphism was in accordance with the Hardy–Weinberg equilibrium in both CAD patients ($p = 0.625$) and control subjects ($p = 0.340$). The distribution of ABCA1 C-565T genotypes was significantly different between the two groups ($p = 0.035$, $\chi^2 = 6.67$) [Table 1]. The frequency of wild-type, homozygote, and homozygote genotypes among the studied groups was 42.7%, 43.6%, and 13.6% in the CAD group; and 54.5%, 40.9%, and 4.5% in the control group [Table 2].

**Table 2:** Genotype and allele frequency of ATP-binding cassette transporter A1 C-565T polymorphism in patients with CAD and control subjects.

| C-565T polymorphism | CAD n = 110 | Control n = 110 | OR | 95% CI | *p*-value |
|---|---|---|---|---|---|
| **Genotypes** | | | | | |
| CC | 47 (42.7) | 60 (54.5) | Ref | - | - |
| CT | 48 (43.6) | 45 (40.9) | 1.36 | 0.78–2.38 | 0.321* |
| TT | 15 (13.6) | 5 (4.5) | 3.83 | 1.29–11.30 | 0.014 |
| **Alleles** | | | | | |
| C allele | 142 (64.5) | 165 (75.0) | Ref | - | - |
| T allele | 78 (35.4) | 55 (25.0) | 1.65 | 1.09–2.49 | 0.017 |

*CAD: coronary artery disease; CC: wild-type; CT: heterozygote; TT: homozygote; OR: odd ratio; CI: confidence interval. *Statistical power = 27.8%. n (%).*

**Table 4:** The association of ABCA1 C-565T polymorphism with the number of stenotic coronary vessels.

| ABCA1 -565C/ T genotypes | 1 SV n = 39 | 2 SV n = 46 | 3 SV n = 25 | *p*-value 2 SV vs. 1SV | *p*-value* 3 SV vs. 1SV |
|---|---|---|---|---|---|
| CC | 19 (48.7) | 20 (43.5) | 8 (32.0) | Ref | Ref |
| CT | 17 (43.6) | 22 (47.8) | 9 (36.0) | 0.820 | 0.773 |
| TT | 3 (7.7) | 4 (08.7) | 8 (32.0) | 0.705 | 0.028 |

*SV: stenotic vessel; ABCA1: ATP-binding cassette transporter A1; CC: wild-type; CT: heterozygote; TT: homozygote.*
**p-values were calculated using Fisher's exact test. n (%).*

**Table 5:** Lipid profile in CAD group across different genotypes of ABCA1 C-565T polymorphism.

| Genotypes | TC, mg/dL | TG, mg/dL | HDL-C, mg/dL | LDL-C, mg/dL |
|---|---|---|---|---|
| CC | 201.4 ± 47.8 | 198.7 ± 81.0 | 38.7 ± 8.8 | 103.7 ± 33.5 |
| CT | 206.1 ± 71.5 | 189.5 ± 88.5 | 39.1 ± 9.6 | 98.1 ± 36.2 |
| TT | 209.3 ± 61.7 | 190.9 ± 72.4 | 37.4 ± 8.4 | 105.2 ± 41.3 |
| *p*-value | 0.606 | 0.737 | 0.622 | 0.881 |

*CAD: coronary artery disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; ABCA1: ATP-binding cassette transporter A1; CC: wild-type; CT: heterozygote; TT: homozygote.*

**Table 6:** Lipid profile in control group according to different genotypes of ABCA1 C-565T polymorphism.

| Genotypes | TC, mg/dL | TG, mg/dL | HDL-C, mg/dL | LDL-C, mg/dL |
|---|---|---|---|---|
| CC | 169.8 ± 71.3 | 169.9 ± 52.0 | 43.4 ± 13.8 | 91.9 ± 36.2 |
| CT | 170.9 ± 40.1 | 152.4 ± 67.8 | 50.6 ± 11.5 | 89.9 ± 28.3 |
| TT | 148.6 ± 29.2 | 152.0 ± 44.3 | 44.5 ± 4.7 | 99.1 ± 31.3 |
| *p*-value | 0.514 | 0.458 | 0.858 | 0.668 |

*HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; ABCA1: ATP-binding cassette transporter A1; CC: wild-type; CT: heterozygote; TT: homozygote.*

In univariate analysis (with genotype CC as reference), the TT genotype was significantly associated with an increased risk of CAD (OR = 3.83; 95% CI: 1.29–11.30; $p = 0.014$), but not the CT genotype ($p = 0.321$) [Table 2]. The frequency of minor T allele of ABCA1 C-565T polymorphism was significantly higher in the CAD group compared with control group (35.45% vs. 25.0%; OR = 1.65; 95% CI: 1.09–2.49; $p = 0.017$). In a multiple binary logistic regression analysis using the study group (CAD group vs. control group) as the dependent variable and using age, sex, TG, TC, HDL-C, LDL-C, smoking, diabetes, hypertension, and C-565T genotypes as covariates, the ABCA1 C-565T polymorphism significantly and independently increased the risk of CAD by 2.1 in a dominant model (CT+TT vs. CC, OR = 2.10; 95% CI: 1.10–4.00; $p = 0.032$) and by 3.1 in a recessive model (TT vs. CT+CC, OR = 3.10; 95% CI: 0.85–10.40; $p = 0.057$). Also, analyzing the role of this polymorphism in CAD occurrence under codominant model (CT vs. CC, OR = 1.36; 95% CI: 0.78–2.38; $p = 0.321$; TT vs. CC, OR = 3.83; 95% CI: 1.29–11.30; $p = 0.014$) revealed a significant association only in homozygote state. Moreover, some other variables including TG ($p = 0.006$), TC ($p < 0.001$), HDL-C ($p < 0.001$), LDL-C ($p = 0.028$), smoking ($p = 0.008$), and hypertension ($p = 0.027$) had a significant and independent effect on the risk of CAD development. However, age ($p = 0.406$), sex ($p = 0.951$), and diabetes ($p = 0.072$) were not significant covariates in regression analysis [Table 3].

The genotypic association of ABCA1 C-565T polymorphism with the severity of CAD (number of stenosis vessels) was investigated [Table 4]. Results revealed significant differences in the distribution of homozygote TT genotype between patients with one and three stenotic vessels ($p = 0.028$), indicating the effect of this polymorphism on the severity of CAD. Furthermore, the genotypic effect of ABCA1 C-565T polymorphism on plasma lipid profile

was investigated [Table 5 and 6]. Results indicated no statistically significant differences in the mean plasma levels of TG, TC, HDL-C, and LDL-C between different genotypes of ABCA1 C-565T polymorphism ($p > 0.050$) in both groups.

## DISCUSSION

We investigated the effect of ABCA1 C-565T polymorphism on the development and severity of CAD in an Iranian subpopulation. The results indicated significant differences in the genotypic ($p = 0.035$) and allelic ($p = 0.017$) distribution of the ABCA1 C-565T polymorphism between the CAD and control groups. Furthermore, the C-565T polymorphism of ABCA1 gene significantly and independently increased the risk of CAD 2.1-fold (95% CI: 1.10–4.00) in a dominant manner ($p = 0.032$). In agreement with our results, Qi et al,[15] identified TT homozygote genotype of ABCA1 C-565T polymorphism as a significant risk factor for CAD development. The possible mechanisms by which ABCA1 C-565T polymorphism induces CAD development may be explained by the decreased rate of cholesterol efflux in carriers of T allele relative to carriers of C alleles, which disturbs the initial step of RCT in cells.[16] The C-565T polymorphism is located in the promoter region of the ABCA1 gene and according to some studies, the T allele of this polymorphism is associated with decreased gene expression levels, decreased membrane expression levels, and reduced RCT activity of the ABCA1 transporter, which collectively predisposes the T allele carriers of this polymorphism for coronary atherosclerosis.[13] Our study is in line with several previously published studies that identified ABCA1 C-565T polymorphism as a risk factor for the development and severity of CAD.[13,15,17–19] However, other studies did not find any association between this polymorphism and CAD risk.[20–22] Also, one study found an inverse association between ABCA1 C-565T polymorphism and coronary heart disease risk.[23] Moreover, another study showed that carriers of the T allele of ABCA1 C-565T polymorphism markedly decreased the risk of vascular death in CAD patients with no apparent effect on HDL-C levels.[12] The reasons for controversial and conflicting results of the genetic association studies are numerous including different genetic background, racial diversity of the study populations, gene-gene and gene-environmental interactions, different selection criteria of the study population, misclassification of phenotypes, and population-specific linkage disequilibrium between markers and causal variants.[24] As stated previously, in our study, the genotype distribution of ABCA1 C-565T polymorphism was consistent with the Hardy–Weinberg equilibrium in both patients with CAD ($p = 0.625$) and control subjects ($p = 0.340$) reflecting the absence of selection bias in our study. Selection bias is a potential source of errors in case-control studies, which may disturb the results of association studies.

Our study showed that patients carrying the TT homozygote genotype of ABCA1 C-565T polymorphism were more prone to develop severe CAD relative to patients carrying the CC genotype, signifying the role of this common polymorphism in determining the severity of CAD in a recessive genetic state. This finding is in agreement with the study by Qi et al,[15] which reported a significant correlation between TT homozygote genotype of ABCA1 C-565T polymorphism and the severity of CAD in a Chinese Han population. In a study of a Japanese population, a significant correlation was documented between the T allele of ABCA1 C-565T polymorphism and severity of CAD.[13] Similar results were also reported in an American population.[25] However, some studies did not report any association between ABCA1 C-565T polymorphism and CAD severity.[26] It seems that the genotypic effects of ABCA1 C-565T polymorphism on the severity of CAD may be influenced by other factors such as genetic background and environmental factors. Moreover, the presence of other gene variants in the ABCA1 gene (not evaluated in our study) may influence the effect of the C-565T polymorphism on the severity of CAD and may explain the controversial results of different studies.

Our study found no significant association between ABCA1 C-565T polymorphism and plasma lipid levels. This finding is in accordance with some previous studies,[19–21,23,27] but in disagreement with others.[14] This result signifies the importance of screening for common polymorphism even in patients with apparently normal lipid profiles. Interestingly, in a mice model that was selectively deficient in leukocyte ABCA1 locus, a significant increase in the CAD occurrence was seen without

considerable change in the plasma HDL-C levels.[28] It should be noted that reduced RCT activity seen in carriers of T allele of ABCA1 C-565T polymorphism may affect the net flux of cholesterol from the vessel wall toward the liver, without necessarily altering plasma lipid levels.[13] Recently, Qi et al,[15] investigated the effect of ABCA1 C-565T polymorphism on the macrophage cholesterol efflux capacity in the CAD patients and reported that the lowest cholesterol efflux activity was seen in patients with TT and CT genotypes compared with patients with CC genotype, suggesting that T allele carriers of ABCA1 C-565T polymorphism are more prone to accumulate intracellular cholesterol without necessarily altering plasma lipid levels.

Our study was conducted in a relatively small subpopulation of an Iranian population, and the generalizability of current results to other Iranian populations may require a further complementary study with a larger sample size. Some limitations could be observed in the present study including: (i) the assay of cellular cholesterol efflux activity (a better indicator of ABCA1 activity) was not performed, (ii) the other polymorphisms of ABCA1 gene and their interactions with CAD development were not investigated, and (iii) the gene expression levels of ABCA1 gene were not determined.

## CONCLUSION

The results of this study are consistent with the notion that ABCA1 C-565T polymorphism may contribute to the development and severity of CAD in an Iranian subpopulation. Moreover, the ABCA1 C-565T polymorphism seems to modify the risk of CAD independent of any change in plasma lipid profile.

*Disclosure*

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