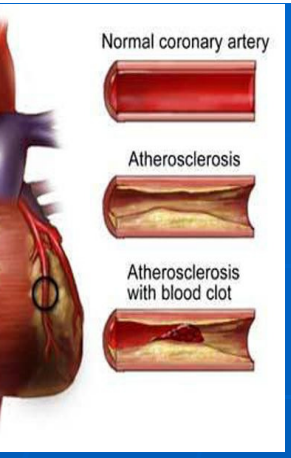
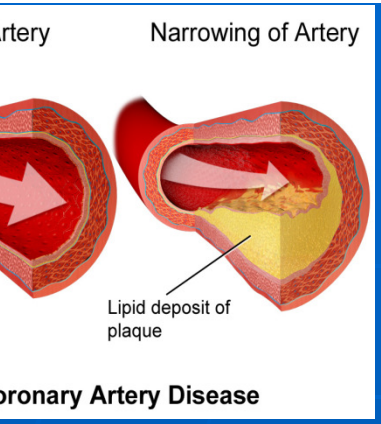


GENETIC MARKERS OF CORONARY ARTERY DISEASE RISK

GALYA ATANASOVA MD, PhD
DOMINIC JAMES

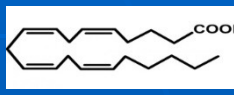


Overview

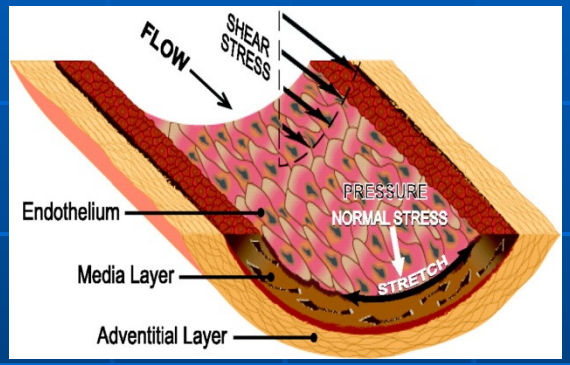
In the present study we analyzed the impact of a genetic variant in CYP2C8 on coronary artery disease (CAD) in the Bulgarian population. We conducted a case-control study to determine whether the common genetic variation rs890293 (CYP2J2*7) in the CYP2J2 gene was associated with the risk of CAD.

Introduction

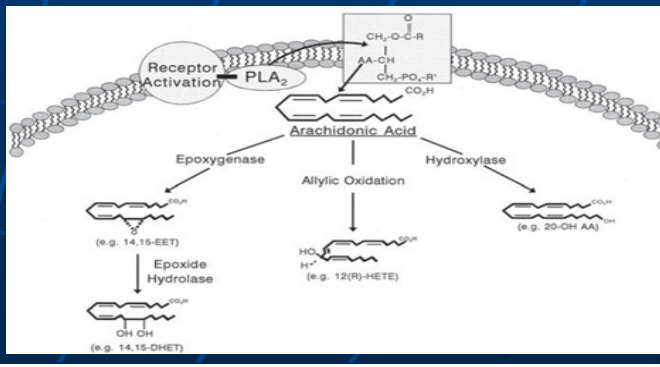
Cytochrome P450 2C8 is a polymorphic enzyme responsible for the biosynthesis of vasoactive substances from arachidonic acid.



Cytochrome P450 (CYP) 2J2 is expressed in the vascular endothelium



and it metabolizes arachidonic acid to biologically active epoxyeicosatrienoic acids (EETs).



Methods

We analyzed 99 patients with CAD and 377 controls for a potential correlation of the *CYP2J2* polymorphism G-50T. 96 of these 99 patients were tested for the presence of polymorphisms CYP2C8.

- To evaluate the genotypes of the samples real time PCR with predesigned TaqMan SNP Genotyping Assays (Applied Biosystem) for rs890293 was used.

- The deviation of allele polymorphism was CYP2J2*7 and CYP2C8*3 respectively according to Hardy-Weinberg equilibrium. The frequency of the T allele was calculated too via the χ^2 test.

Results

The main dichotomous and nondichotomous and clinical characteristics of the study group are shown in table 1 and table 2.

Table 1. Dichotomous clinical characteristics of the group

Characteristic	Number	Percentage
Men	60	60.61
Women	39	39.39
Smokers	44	44.44
Hereditary	40	40.40
Hypertension	92	92.93
Type 1 diabetes	2	2.02
Type 2 diabetes	25	25.25

Table 2. Nondichotomous clinical characteristics of the group.

Characteristic	Average	Average deviation
BMI [kg/m^2]	27.98	5.13
Triglyceride levels [mmol/l]	2.13	0.77
Cholesterol levels [mmol/l]	5.90	0.98
HDL [mmol/l]	1.42	0.62

The frequency of genotypes of the T allele CYP2J2*7 and CYP2C8*3 s shown in tables 3 and 4.

Table 3. The frequency of genotypes of the T allele in CYP2J2 * 7.

Alleles	Group with coronary artery disease- 99		Control group - 377		Total – 476	
	Number	Percentage	Number	Percentage	Number	**Percentage**
TT	2	2.02	2	0.53	4	**0.84**
TG	12	12.12	39	11.57	51	**10.71**
TT or TG	14	14.14	41	12.10	55	**11.55**
GG	85	85.86	336	87.90	421	**88.45**
Frequency	0.0808	8.08	0.057	5.7	0.062	**6.2**
p-value	**0.0670**		**0.4586**		**0.0868**	

In the group of people with MI, the percentage of these T-allele is slightly greater than in the control group - 14.14% respectively versus 12.10% of patients with T-allele (Table 3). The frequency o presence of the T-allele was also greater in the group with infarction (8.08%) than in the control group (5.7%).

The obtained p-value for the statistical significance of the hypothesis (relating to the distribution of the T-allele in CYP2J2 * 7), taking into account Hardy-Weinberg Equilibrium, is greater than 0.05 and therefore for all groups of this hypothesis cannot be rejected.

Table 4. The frequency of genotypes of CYP2C8 * 3.

Alleles	Group with coronary artery disease - 96		Control group - 363		Total – 459	
	Number	Percentage	Number	Percentage	Number	Percent
	2	2.08	3	0.83	5	**0.84**
	26	27.08	67	18.46	93	**10.7**
r TG	28	29.16	70	19.29	98	**11.5**
	68	70.84	293	80.71	361	**88.4**
uency	0.1562	15.62	0.1006	10.06	0.1122	**11.2**
lue	**0.7901**		**0.6974**		**0.7153**	

The resulting p-values for both polymorphism (for CYP2C8 * 3, p = 0.7901 and p = 0.0670 CYP2J2*7) indicates that the distribution of T allele CYP2C8*3 with high probability lies closer to Hardy Weinberg Equilibrium than in the CYP2J2 * 7 gene (tables 3, 4).

An analysis of the connection between gender and the likelihood of CAD among polymorphisms in the CYP2J2 * 7 and CYP2C8 * 3 is made. The results are shown in table 5 and table 6.

Table 5. Association of the T-allele CYP2J2 * 7 with CAD.

CAD / T- allele	Yes	No	Total
Yes	14	41	**55**
No	85	336	**421**
Total	**99**	**377**	**476**

The obtained p-value is p=0.3656 which show that the hypothesis of no association can not be rejected. The odds ratio (OR) for polymorphism in the CYP2J2 * 7 is 1.35 with CI=0.7034÷2.5900. The results show that there is not evidence for association between the T-allele and CAD.

Table 6. Association of the T-allele CYP2C8 * 3 with CAD.

CAD / T- allele	Yes	No	Total
Yes	28	70	**98**
No	68	293	**361**
Total	**96**	**363**	**459**

The obtained p-value is p=0.0356 which show that the hypothesis of no association have to be rejected. The chances for people with T-allele polymorphism in the CYP2C8 * 3, CAD occur on average 1.7 times higher than those who did not carry this allele. CI of OR (1.0334÷2.8746) with 95% probability. CI indicated that it could be argued with a 95% probability that the presence of T allele in CYP2C8 * 3 increases the risk of CAD.

An analysis of the connection between gender and the likelihood of CAD among the carriers of the T allele polymorphisms in the CYP2J2 * 7 and CYP2C8 * 3 is made. The results are shown in table 7 and table 8.

The obtained p-value and OR are p=0.8005 and OR=1.1719 with CI=0.3423÷4.011. The analysis shows that gender is not a risk factor for CAD among T allele CYP2J2 * 7 carriers.

Table 7. Association between gender and CAD among carriers of the T allele in the CYP2J2 * 7.

type 2 diabetes T- allele	Yes	No	Total
Yes	2	12	14
No	23	62	85
Total	25	74	99

Table 8. Association between gender and CAD among carriers of the T allele in CYP2C8 * 3

type 2 diabetes T- allele	Yes	No	Total
Yes	5	23	28
No	17	51	68
Total	22	74	96

analysis shows that gender is not a CAD risk factor among T allele CYP2C8 * 3 carriers.

Analyzed is the relationship between gender and the likelihood of CAD among participants without T-allele polymorphisms in the CYP2J2*7 and CYP2C8*3. The results are shown in table 9 and table 10.

Table 9. Association between hereditary and CAD among carriers of the T allele in the CYP2J2 * 7.

hereditary / T- allele	Yes	No	Total
Yes	8	6	**14**
No	32	53	**85**
Total	**40**	**59**	**99**

e obtained statistical parameters are p=0.1091 and OR=1.4917 =0.9130÷2.4374. The obtained values shows that it is unlikely that gender is a tor for CAD among T allele CYP2J2 * 7 carriers.

Table 10. Association between gender and CAD among participants without T-allele in CYP2C8 * 3.

hereditary T- allele	Yes	No	Total
Yes	10	18	**28**
No	28	40	**68**
Total	**38**	**58**	**96**

The obtained statistical parameters are p=0.1547 and OR=1.4781 with CI=0.8612÷2.5369. The obtained values shows that it is unlikely sex to influence on CAD chances among T allele CYP2C8 * 3 carriers.

Table 11 and Table 12 shows the results of the association between the presence of the T allele and smoking respectively CYP2J2 * 7 and CYP2C8 * 3.

Table 11. Association between the T allele in the CYP2J2 * 7 and smoking in the group with CAD.

Smoker / T- allele	Yes	No	Total
Yes	5	9	**14**
No	39	46	**85**
Total	**44**	**55**	**99**

The obtained statistical parameters are p=0.4780 and OR=0.6553 with CI=0.2027÷2.1187. The obtained values shows that there isn't association between smoking and CAD among T allele CYP2J2 * 7 carriers.

Table 12. Association between the T - allele in CYP2C8 * 3 and smoking group with CAD.

Smoker / T- allele	Yes	No	Total
Yes	17	11	**28**
No	26	42	**68**
Total	**43**	**53**	**96**

The obtained p-value is p=0.0441 and consequently there is statistica significant association between smoking and CAD among T allele CYP2C8 * 3 carriers. The odds ratio is 2.4965 with CI 1.0125÷6.1555. The results indicate that the chances for CAD are 2.5 times greater to smokers.

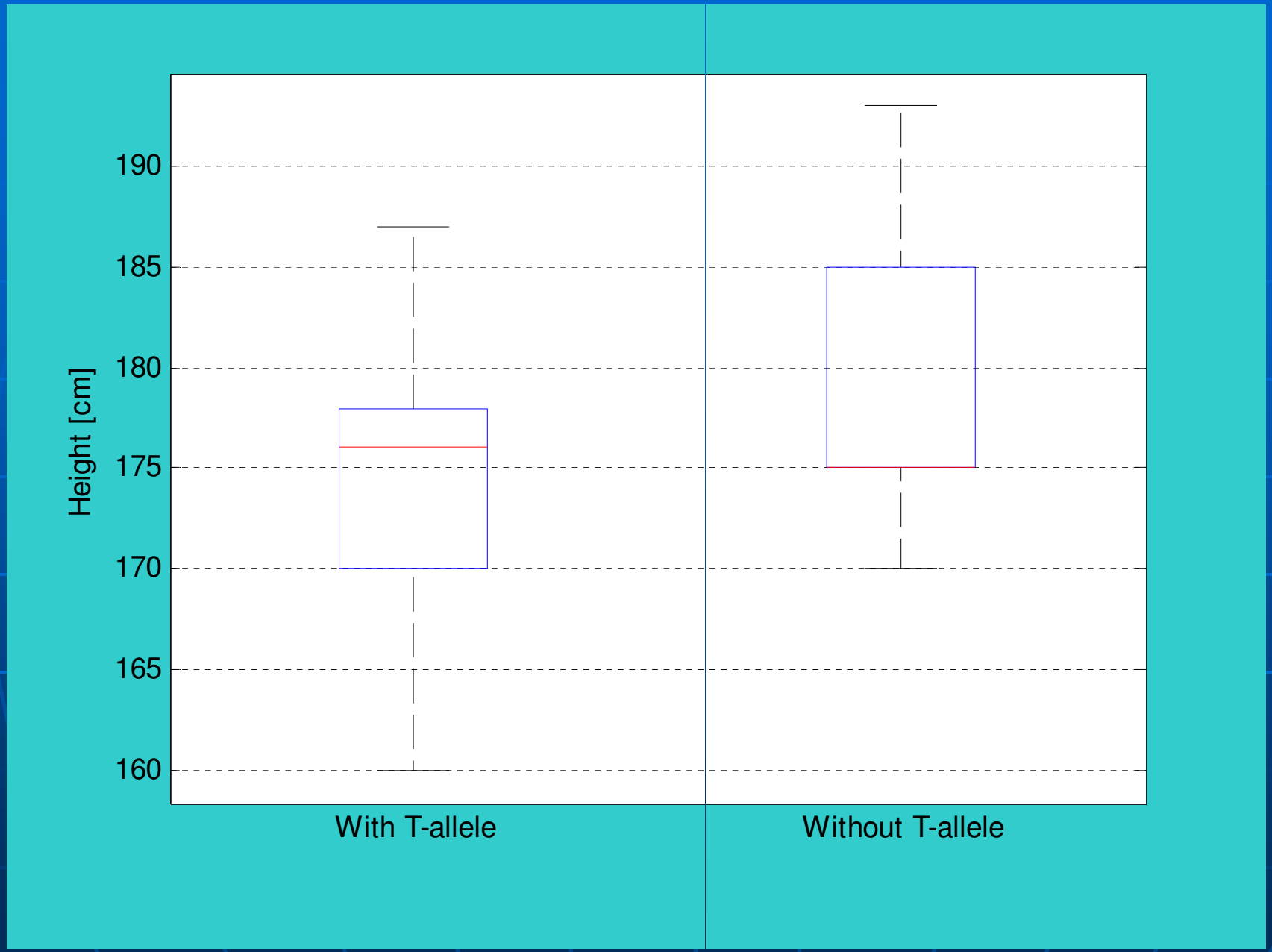


Fig 1. ANOVA test of men height for groups with and without T-allele in CYP2C8 * 3.

Conclusions

The analysis of results shows that polymorphism CYP2C8 * 3 is more important for the occurrence of CAD compared with CYP2J2 * 7 in the study. Demonstrates a statistically significant association between the presence of the T-allele in CYP2C8 * 3 and smoking group with CAD (OR = 2.4965, CI = 1.0125÷6.1555). The risk for CAD is 2.5 times greater for smokers.

The one-way ANOVA test showed a difference in average height only for men with and without T allele in CYP2C8*3 (p=0. 0272 and F-statistic F=5.1314).

THANK YOU