

# The association of interleukin-6 gene with obesity in patients with coronary artery disease

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**The aim** of this study was to estimate value of a polymorphic locus *C-174G* of interleukin-6 gene in obesity development in patients with coronary artery disease.

**Materials and methods.** 222 patients with coronary artery disease and obesity were included in this study. The research of an allelic *C-174G* polymorphism of interleukin-6 gene was conducted by PCR method with electrophoretic detection of results with use of reactants SNP-EKSPRESS ("Sintol", Russian Federation).

**Results.** Development of obesity in patients with coronary artery disease has been connected with *G* gene (odds ratio = 1.58, 95 % confidence interval = [1.12–2.24],  $\chi^2 = 6.9$ ;  $p < 0.05$ ) and *G/G* genotype (odds ratio = 1.98, 95 % confidence interval = [1.25–3.16],  $\chi^2 = 8.4$ ;  $p < 0.05$ ) polymorphic locus of *C-174G* of interleukin-6 gene. The genotype *G/G* was reliably more frequent in patients with coronary artery disease and stage III of obesity by 15.26 % and 8.45 %, than in patients with the accompanying I and II stages of obesity ( $p < 0.05$ ). In its turn, *C/G* genotype in patients with coronary artery disease and the III stage of obesity occurred 11.21 % less, than in patients with the I stages of obesity ( $p < 0.05$ ). Allele *C*, *G* and genotype *C/C* had unreliable distribution in patients with coronary artery disease depending on obesity degree ( $p < 0.05$ ).

**Conclusions.** This study has shown that the allele of *G* and *G/G* genotype of polymorphic locus *C-174G* of interleukin-6 gene is associated with development and progression of obesity in patients with coronary artery disease.

**Key words:**

myocardial ischemia, obesity, interleukin-6 gene.

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## Асоціація гена інтерлейкіна-6 з ожирінням у пацієнтів з ішемічною хворобою серця

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**Мета роботи** – оцінити значення поліморфного локусу *C-174G* гена інтерлейкіна-6 у розвитку ожиріння у хворих з ішемічною хворобою серця.

**Матеріали та методи.** Комплексно обстежили 222 пацієнти з ішемічною хворобою серця та ожирінням. Групу порівняння становили 115 хворих на ІХС із нормальною масою тіла. До контрольної групи увійшло 35 практично здорових осіб. Групи порівняні за віком і статтю. Діагноз встановлювався згідно з чинними наказами МОЗ України. Дослідження алельного поліморфізму *C-174G* гена інтерлейкіна-6 здійснили методом полімеразної ланцюгової реакції з електрофоретичною детекцією результатів із використанням наборів реактивів «SNP-EKSPRESS» («Синтол», Російська Федерація).

**Результати.** Розвиток ожиріння у хворих на ІХС був пов'язаний з алеллю *G* (відношення шансів = 1,58, 95 % довірчий інтервал = [1,12–2,24],  $\chi^2 = 6,9$ ;  $p < 0,05$ ) та *G/G* генотипом (відношення шансів = 1,98, 95 % довірчий інтервал = [1,25–3,16],  $\chi^2 = 8,4$ ;  $p < 0,05$ ) поліморфного локусу *C-174G* гена інтерлейкіна-6. Генотип *G/G* виявлявся вірогідно частіше у хворих з ішемічною хворобою серця та ожирінням III стадії на 15,26 % і 8,45 %, ніж у хворих із супутнім ожирінням I та II стадій ( $p < 0,05$ ). Генотип *C/G* у хворих з ішемічною хворобою серця та ожирінням III стадії, своєю чергою, виявлявся рідше на 11,21 %, ніж у хворих з ожирінням I стадії ( $p < 0,05$ ). Алелі *C*, *G* і генотип *C/C* мали невіргодний розподіл у хворих на ішемічну хворобу серця залежно від ступеня ожиріння ( $p > 0,05$ ).

**Висновки.** Алель *G* і *G/G* генотип поліморфного локусу *C-174G* гена інтерлейкіна-6 пов'язані з розвитком і прогресуванням ожиріння у хворих на ішемічну хворобу серця.

**Ключові слова:**

ішемічна хвороба серця, ожиріння, ген інтерлейкіна-6.

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## Ассоциация гена интерлейкина-6 с ожирением у пациентов с ишемической болезнью сердца

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**Цель работы** – оценить значение полиморфного локуса *C-174G* гена интерлейкина-6 в развитии ожирения у больных с ишемической болезнью сердца.

**Материалы и методы.** С целью исследования проведено комплексное обследование 222 больных с ишемической болезнью сердца и ожирением. Группу сравнения составили 115 больных ишемической болезнью сердца с нормальной массой тела. В контрольную группу вошло 35 практически здоровых лиц. Группы были сопоставимы по возрасту и полу. Диагноз устанавливался в соответствии с действующими приказами Минздрава Украины. Исследование аллельного полиморфизма *C-174G* гена интерлейкина-6 проводили методом полимеразной цепной реакции с электрофоретической детекцией результатов с использованием наборов реактивов «SNP-ЭКСПРЕСС» («Синтол», Российская Федерация).

**Результаты.** Развитие ожирения у больных ишемической болезнью сердца было связано с геном *G* (отношение шансов = 1,58, 95 % доверительный интервал = [1,12–2,24],  $\chi^2 = 6,9$ ;  $p < 0,05$ ) и *G/G* генотипом (отношение шансов = 1,98, 95 % доверительный интервал = [1,25–3,16],  $\chi^2 = 8,4$ ;  $p < 0,05$ ) полиморфного локуса *C-174G* гена интерлейкина-6. Генотип *G/G* встречался достоверно чаще у больных с ишемической болезнью сердца и ожирением III стадии на 15,26 % и 8,45 %, чем у больных с сопутствующим ожирением I и II стадий ( $p < 0,05$ ). В свою очередь, генотип *C/G* у больных

**Ключевые слова:**

ишемическая болезнь сердца, ожирение, ген интерлейкина-6.

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с ишемической болезнью сердца и ожирением III стадии встречался реже на 11,21 %, чем у больных с ожирением I стадии ( $p < 0,05$ ). Аллели C, G и генотип C/C имели недостоверное распределение у больных ишемической болезнью сердца в зависимости от степени ожирения ( $p > 0,05$ ).

**Выводы.** Аллель G и G/G генотип полиморфного локуса C-174G гена интерлейкина-6 связаны с развитием и прогрессированием ожирения у больных ишемической болезнью сердца.

## Introduction

There is little data on association of genes coding pro-inflammatory cytokines polymorphism with cardiovascular diseases (CD) development in the literature, and these only few researches devoted to interrelation between polymorphisms with risk of development and origin of chronic heart failure (CHF) progression in patients with coronary artery disease (CAD).

So, S. N. Shilov and coworkers showed in their work that polymorphic options of interleukin (*IL*)-1 $\beta$  (C + 3953T) genes, tumor necrosis factor (TNF)- $\alpha$  (G-308A), endothelial nitric oxide synthase (eNOS) (Glu298Asp) not only are the determinants of the increased risk of CHF development in ischemic heart disease patients, but also are associated with severity and character of heart failure course in this category of patients. Besides, it has been proved that polymorphic loci of *IL*-1 $\beta$  (C+ 3953T) gene are associated with expression of heart inotropic function disturbances and left ventricle remodelling. It is necessary to notice that the research was carried out with participation of Caucasian race patients, the Novosibirsk population. In total 226 ischemic heart disease patients with CHF I–IV functional class (FC) were examined, among them – 149 men and 77 women aged from 45 up to 65 years. Control group consisted of 136 people, among them – 63 men and 73 women aged from 45 up to 65 years without cardiovascular pathology and serious chronic illness [1]. 266 patients with CHF and EF lower than 40 % have been included in other research, no associations between TNF- $\alpha$  plasma concentration and TNF- $\alpha$  (308 A/G, 238 A/G, TNF beta NcoI and 3TACE) gene polymorphism have been observed [2].

L. Spinarova et al. [3] studied a polymorphism of G8002A and gene of *endothelin-1* (EDN1) 3A/4A, and also TNF- $\alpha$  – A308G, A238G, FNO- $\beta$  NcoI and 3TACE genes polymorphism in patients with CHF of ischemic genesis and diabetes mellitus. The research included 224 patients of Caucasian race (176 men and 48 women, the average age was 55 years), with CHF II–IV FC and proved reduction of left ventricle ejection fraction less than 40 %. Authors didn't find relationship between plasma concentration of endothelin-1 and G8002A ( $p = 0,87$ ,  $p = 0,81$ ) and 3A/4A ( $p = 0,871$ ,  $p = 0,749$ ) EDN1 gene polymorphism. Also interrelations between TNF- $\alpha$  plasma concentration and polymorphic options of TNF- $\alpha$ ,  $\beta$  and TNF- $\alpha$ -turning enzyme genes haven't been observed. However it has been established that an allele A of G8002A polymorphism in comparison with G gene was reliably more frequent in the patients after MI and/or had ischemic disease of the lower extremities. In patients with dilatation cardiomyopathy the prevalence of this or that EDN1 gene polymorphic option hasn't been revealed. It has been concluded that EDN1 and TNF- $\alpha$  gene polymorphic options aren't important genetic determinants in patients with CHF, and their plasma concentration depends rather on the HF severity.

Wang et al. [4] suggested a correlation between – 174 G > C and coronary artery disease, whereas Ghazouani et al. [5] and Tong et al. [6] did not find this correlation, although all 3 studies were aimed to assess coronary artery disease.

Discrepancy of the obtained data is probably connected with lack of the large randomized researches devoted to this problem, once again confirms need of further studying of genes coding pro-inflammatory cytokines polymorphism and also their influence on CD and CHF formation and progression.

**The purpose** – to estimate the value of interleukin-6 gene C-174G polymorphic locus in the development of obesity in patients with coronary artery disease.

## Materials and methods

For investigation a comprehensive examination of 222 patients with CAD and obesity treated in cardiologic unit of the Kharkiv City Hospital № 27 which is the basic medical institution of Department of Internal Medicine № 2 and Clinical Immunology and Allergology of Kharkiv National Medical University HM of Ukraine was carried out. The comparison group included 115 CAD patients with normal body weight. 35 almost healthy people formed the control group. In addition CAD patients and obesity patients had been divided into subgroups depending on degree of obesity: the first subgroup was composed of 80 patients with obesity I stage, the second included 71 patients with obesity II stage, the third – 71 patients with obesity III stage. Groups were comparable in age and sex. The research didn't include patients with the serious accompanying pathology of respiratory organs, digestive system, kidneys and persons with oncologic diseases.

The diagnosis was established according to the existing orders of HM of Ukraine.

General clinical and instrumental examinations were carried out for all patients. The body weight index (BWI) (Quetelet's index) was used to characterize obesity and was calculated on the basis of the following formula:

$$\text{weight (kg) / body height (sq. m)}$$

The research of interleukin-6 C-174G gene allelic polymorphism was carried out by PCR method with electrophoretic detection of results using "SNP-EKSPRESS" sets of reagents produced by CJSC "Sintol" (Russian Federation). Correctness of genotypes frequencies distribution was defined by compliance with G. Hardy–V. Weinberg equilibrium ( $p_i^2 + 2 p_i p_j + p_j^2 = 1$ ). According to the Helsinki Declaration all patients were informed of the clinical trial and have given their consent for studied gene polymorphism identification.

Statistical data processing was realized by means of Statistic software application, version 6.0. For comparison of alleles and genotypes frequencies distribution between groups criteria  $\chi^2$  of Pearson and Fischer was used. Odds ratio (OR) for determination of diseases development

risk was calculated. OR = 1 was regarded as absence of associations; OR > 1 – as the positive association; OR < 1 – as the negative association of allele or genotype with disease (low risk of disease development). The confidence interval (CI) represented the interval of values within which was 95 % probability of OR prognostic value. Statistically significant differences have been considered in case of  $p < 0.05$ .

## Results

Development of obesity in patients with CAD has been connected with G gene (OR = 1.58, 95 % CI = [1.12–2.24],  $\chi^2 = 6.9$ ;  $p < 0.05$ ) and G/G genotype (OR = 1.98, 95 % CI = [1.25–3.16],  $\chi^2 = 8.4$ ;  $p < 0.05$ ) polymorphic locus C-174G of IL-6 gene (Table 1).

The study of alleles and genotypes of IL-6 gene C-174G polymorphic locus frequency distribution in patients with CAD depending on BMI showed reliable increase in frequency of genotype G/G detection according to increase in body weight (Table 2).

The genotype G/G was reliably more frequent in patients with coronary artery disease and stage III of obesity by 15.26 % and 8.45 %, than in patients with the accompanying I and II stages of obesity ( $p < 0.05$ ). In its turn, C/G genotype in patients with coronary artery disease and the III stage of obesity occurred 11.21 % less, than in patients with the I stages of obesity ( $p < 0.05$ ). Allele C, G and genotype C/C had unreliable distribution in patients with coronary artery disease depending on obesity degree ( $p < 0.05$ ).

## Discussion

Inflammation plays a very important role in atherosclerosis and cardiovascular diseases development. IL-6 is primarily secreted into serum and binds to receptor alpha (IL-6R- $\alpha$ ) to mediate a transcriptional inflammatory response during acute or chronic inflammatory process. Second, IL-6 stimulates the migration and proliferation of vascular smooth muscle cells and reconstructs vessels. Third, IL-6 regulates blood pressure by stimulating the sympathetic nervous system and controlling the angiotensinogen expression, resulting in a high angiotensin II concentration and its receptors. Fourth, IL-6 increases the concentration of Ca<sup>2+</sup> in vascular smooth muscle cells and causes vasoconstriction. Last, despite the direct effect on blood pressure, IL-6 is associated with obesity, CAD, diabetes mellitus, [7] and catecholamine release, all of them can cooperate to promote the occurrence and development of hypertension. Thus, the progress of CAD may be affected by anything that interferes with the copy, transcription and translation of the IL-6 gene or secretion, migration, and proliferation of IL-6 protein.

CAD is a major cause of morbidity and mortality, much international effort has been expended to detect risk factors, both heritable and environmental [8]. One of these, obesity, is associated with CAD. Genetic factors play an important role in the primary obesity development. Recent studies concentrate on IL-6 gene polymorphisms influence on certain medical conditions development. The relation between some genetic variant and obesity development seems to be more and more precisely documented.

A small number of works are devoted to studying of IL-6 gene polymorphic locus C-174G role in obesity

**Table 1.** Value allele G and IL-6 gene G/G genotype polymorphic locus C-174G in obesity development in patients with CHD

Genetic markers	OR (95 % CI)
Allele G	1.58 (1.12–2.24) $\chi^2 = 6.9$ ; $p < 0.05$
Genotype G/G	1.98 (1.25–3.16) $\chi^2 = 8.4$ ; $p < 0.05$

**Table 2.** Frequency of alleles and genotypes of IL-6 gene polymorphic locus C-174G detection depending on BMI in patients with CAD and obesity

Genetic markers	1 group Obesity I st. (n = 80)	2 group Obesity II st. (n = 71)	3 group Obesity III st. (n = 71)
Allele C	24 (30 %)	19 (26.76 %)	20 (28.17 %)
Allele G	56 (70 %)	52 (73.24 %)	51 (71.83 %)
Genotype C/C	10 (12.5 %)	8 (11.27 %)	6 (8.45 %)
Genotype C/G	27 (33.75 %)	20 (28.17 %)	16 (22.54 %)*
Genotype G/G	43 (53.75 %)	43 (60.56 %)*	49 (69.01 %)*#

\*: reliability of differences with the 1 group ( $p < 0.05$ ); #: reliability of differences with the 2 group ( $p < 0.05$ ).

development and their results show contradictory data. Our results, unlike what was reported in Finland [9], can be compounded with results which were received after carrying out researches among Americans and Spaniards [10], which showed that homozygotes with G/G-genotype bound to insulin resistance, type 2 diabetes mellitus and obesity.

Confusing data obtained by authors studying the influence of G 174C polymorphism on the incidence of diabetes and obesity might be explained by difficulties in selection of control and experimental groups. As there are so many divergences and uncertainties, there is an urgent need to study associations between polymorphisms of genes encoding proinflammatory cytokine genes and various obesity risk factors.

## Conclusions

The allele of G and G/G genotype of polymorphic locus C-174G of interleukin-6 gene is associated with development and progression of obesity in patients with coronary artery disease.

**The perspectives of further scientific research** in this direction is to study the best ways of pharmacological therapy in patients with CAD and obesity.

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