

Genetic predisposition for the development of complications in patients after coronary artery stenting

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Abstract

In the review the authors analyzed the literature data on the state of knowledge of the problems of genetic polymorphisms CYP2C19 gene response to clopidogrel in patients with acute coronary syndrome. Despite on the technological advances and the widespread use of coronary stenting, restenosis at the site of angioplasty remains the main factor limiting its long-term effectiveness.

We made the literature review of the state of the study of the genetic polymorphism of the CYP2C19 gene for a response to clopidogrel in patients with acute coronary syndrome and percutaneous coronary intervention. To achieve this goal, a systematic search and subsequent analysis of publications and online resources were carried out. All publications are indexed in the PubMed, Medline, e-Library, Cooglescholar.

Key words: coronary heart disease, percutaneous coronary angioplasty, stenting, restenosis, clopidogrel, CYP2C19, acute coronary syndrome, gene polymorphism

КОРОНАРДЫҚ АРТЕРИЯ СТЕНТТЕУДЕН КЕЙІНГІ НАУҚАСТАРДА АСҚЫНУЛАР ДАМУЫНЫҢ ГЕНЕТИКАЛЫҚ БЕЙІМДІЛІГІ

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ТҰЖЫРЫМДАМА

Берілген әдеби шолуда авторлар жедел тәждік синдромы бар науқастардағы клопидогрел қабылдау кезіндегі CYP2C19 гендік полиморфизмінің мәселелері туралы білімінің жай-күйі жайлы әдебиеттерге талдау жасады. Технологиялық жетістіктерге қарамастан, ангиопластика орнында рестеноз даму ұзақ мерзімді тиімділігін шектейтін негізгі фактор болып қала береді.

Жедел тәждік синдромы және терішілік тәждік араласудан кейінгі науқастарда клопидогрелге жауап беру үшін CYP2C19 генінің генетикалық полиморфизмін зерттеу жағдайына әдебиеттер шолуын жасадық. Осы мақсатқа жету үшін жүйелі іздеу және жарияланымдар мен интернет-ресурстарға талдау жүргізілді. Барлық жарияланымдар PubMed, Medline, электрондық кітапхана, Cooglescholar индекстелген.

Негізгі сөздер: жүректің ишемиялық ауруы, терішілік тәждік араласу, стенттеу, рестеноз, клопидогрел, CYP2C19, жедел тәждік синдром, гендік полиморфизмі

ГЕНЕТИЧЕСКАЯ ПРЕДРАСПОЛОЖЕННОСТЬ РАЗВИТИЯ ОСЛОЖНЕНИЙ У БОЛЬНЫХ ПОСЛЕ СТЕНТИРОВАНИЯ КОРОНАРНЫХ АРТЕРИИ

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РЕЗЮМЕ

В обзоре авторы проанализировали литературные данные о состоянии знаний о проблемах генетического полиморфизма ответа гена CYP2C19 на клопидогрель у пациентов с острым коронарным синдромом. Несмотря на технический прогресс и широкое использование коронарного стентирования, рестеноз в месте ангиопластики остается основным фактором, ограничивающим его долговременную эффективность.

Мы сделали обзор литературы о состоянии изучения генетического полиморфизма гена CYP2C19 для ответа на клопидогрель у пациентов с острым коронарным синдромом и чрескожным коронарным вмешательством. Для достижения этой цели был проведен систематический поиск и последующий анализ публикаций и онлайн-ресурсов. Все публикации индексируются в PubMed, Medline, электронной библиотеке, Cooglescholar.

Ключевые слова: ишемическая болезнь сердца, чрескожное коронарное вмешательство, стентирование, рестеноз, CYP2C19, клопидогрель, острый коронарный синдром, генетический полиморфизм

Introduction

The problem of treatment of coronary heart disease (CHD) is one of the top priorities of the world and national healthcare, as it is on the first place among the causes of cardiovascular mortality [1].

Endovascular interventions have opened a new stage in cardiology, significantly expanding the possibilities of CHD treating. According to the intensity of development, coronary stenting outstripped all previous technologies of coronary angioplasty [2]. Despite significant initial success, the widespread introduction of coronary stenting into clinical practice led to not so optimistic long-term results obtained in the first randomized trials. Long-term results forced cardiologists to change their attitude to coronary stenting and approach to endovascular treatment more differentially [3].

This method has revealed a number of factors limiting its effectiveness and application, the main one of which remains restenosis of the coronary arteries, which occurs in 6-12 months after stent implantation [2].

In general, cardiovascular diseases in Kazakhstan are responsible for almost one-third of all deaths. In the structure of mortality from diseases of the circulatory system, 34% are the patients with coronary heart disease (CHD), of whom more than 30% are active working age persons (18-65 years) [4]. The prognosis and outcome of the disease is directly influenced by timely diagnosis, prevention of complications and early conduction of myocardial revascularization [5].

In large-scale clinical trials [6], it was found that asymptomatic restenosis occurs in approximately 48-58% of patients with Percutaneous Coronary Intervention (PCI). P. Ruygrok et al. (2001) evaluated clinical and angiographic factors associated with asymptomatic restenosis. Restenosis developed in 16% from 1 469 stented patients, while in 58% of them it was asymptomatic. Multivariate analysis of this group showed that male sex prevails among restenotic patients, and predictors of asymptomatic restenosis may have a minor degree of lesion during the first 6 months [6].

Genetic factors associated with complications while taking clopidogrel

Clopidogrel is a prodrug derived from thienopyridine, which requires biotransformation in the liver to the active metabolite. Clopidogrel selectively and irreversibly inhibits the purinergic receptor P2RY12 and, thus, leads to the loss of platelet aggregation ability throughout their life (~ 7-10 days). Only 15% of the prodrug is converted to the active substance; the remaining 85% are hydrolyzed by esterases to inactive forms. Conversion of clopidogrel to its active metabolite requires two consecutive processes of oxidation involving hepatic enzyme cytochrome P450 (CYP450), e.g., CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5 [7], preferably CYP2C19 enzyme. Cytochrome P450 CYP2C19 gene belongs to the family 2, subfamily C, polypeptide 19 and located in the cluster of genes cytochrome P450 (CYP2C18-centromere-CYP2C19-CYP2C9-CYP2C8-telomeres) on chromosome 10q23.33. CYP2C19 enzyme is involved in the metabolism of a large number of clinically important drugs such as antidepressants [8], benzodiazepine [9], mephenytoin [10], proton pump inhibitors (PPIs) [11], as well as prodrugs clopidogrel with antiplate activity [12].

Currently, it is unclear how the changes in platelet aggregation revealed *Ex vivo* resulting from simultaneous application of omeprazole and clopidogrel to the clinically significant outcome difference are unclear [13].

CYP2C19 gene has nine exons and is highly polymorphic, with more than 25 variants of alleles (they are marked with asterisks*), currently registered in the Committee for the Nomenclature of Cytochrome P450 alleles <http://www.cypalleles.ki.se/CYP2C19.htm>.

In addition, information on detailed mapping of CYP2C19 alleles and a list of associated drugs and diseases is available at [http://www.pharmgkb.org/search/annotated Gene/CYP2C19/variant.jsp](http://www.pharmgkb.org/search/annotated%20Gene/CYP2C19/variant.jsp).

Clopidogrel resistance (CR) is determined by a decrease in platelet accumulation rate of less than 10% compared with the initial level after treatment with clopidogrel [6-9]. CR is believed to be critically involved in recurrent myocardial infarction after antiplatelet therapy [20]. A weak response of clopidogrel predicts a weak antiplatelet effect of treatment in 4-30% of patients, while platelet hypersensitivity is the main cause of repeated ischemic events and even death of patients with ACS. A recent study of a healthy population of Hulot et al. [30] showed that a sharp decrease in platelet accumulation rate after clopidogrel administration in normal patients with the wild-type CYP2C19 allele (CYP2C19*1/*1), which was absent among carriers of the zero allele (CYP2C19*1/*2). CYP2C19 polymorphism is associated with the bioavailability of active clopidogrel metabolites.

The wild type of CYP2C19*1 allele is associated with a functional (physiological) metabolism mediated by CYP2C19 enzyme. The most common allele with a decreased function is CYP2C19*2, the frequency of this allele is about 12% for Caucasians, 12% – for African Americans and 29-35% – for Asians.

According to other sources [14], the prevalence of the allele with CYP2C19*2 genotype is about 25-30% in Europeans and 50-60% in Asians.

Alleles with reduced or absent enzyme activity (for example, *3 – *8) were also detected. The frequency of CYP2C19*3 allele in most populations is below 1%; this allele is most common among Asians (2-9%) [15]. The less common CYP2C19 alleles associated with the lack or decreased activity of the enzyme are CYP2C19*4 (rs28399504), *5 (rs56337013), *6 (rs72552267), *7 (rs72558186), and *8. Frequency of occurrence of these variants, as a rule, is less than 1% [15, 16] and their definition is of no clinical significance.

CYP2C19 alleles with functions loss are inherited in an autosomal-codominant type. Thus, heterozygotes (for example, or *1/*2 and *1/*3) have a response to clopidogrel, which is intermediate, between the response of wild-type homozygotes (eg, *1/*1) and the homozygous response of alleles to loss of function (*2/*2) or complex heterozygotes (*2/*3) [16].

The first meta-analysis of Russian studies of clopidogrel pharmacogenetics in 2015 revealed that the presence of CYP2C19*2 polymorphism significantly increases the risk of complications such as cardiovascular mortality / myocardial infarction / stent thrombosis / ischemic stroke / transient ischemic attack (Chernov A.A., 2015). The data obtained are consistent with foreign meta-analyses on relevant topics (T. Bauer, 2011; Mao L., 2013).

Based on the ability of CYP2C19 substrates to metabolize people can be classified as enhanced metabolizers (UM), extensive metabolizers (EM), intermediate metabolizers (IM) and attenuated metabolizers (AM). Extensive metabolizers are homozygous for the CYP2C19*1 allele, which are associated with functional (physiological) metabolism mediated by CYP2C19. The genotype of the intermediate metabolizers

consists of one wild type allele and one variant of the allele that codes for the decrease or absence of the enzyme function (for example, *1/*2, *1/*3), which leads to a decrease in the activity of CYP2C19 [17]. People associated with impaired metabolizers have two alleles with loss of function (eg, *2/*2, *2/*3, *3/*3), resulting in a marked decrease or no activity of their CYP2C19 [16].

It should be noted that some researchers use a different nomenclature, including «homozygous extensive metabolizers» (for example, *1/*1), sometimes they are called persons with «fast metabolism»; and also «heterozygous extensive metabolizers» (for example, *1/*2) and «slow metabolizers» (for example, *2/*2). Regardless of the nomenclature system used, the rate of occurrence of slow CYP2C19 metabolizers is about 2-5% in Caucasians and African Americans and about 15% in Asians [18].

Individuals who have one or two alleles *17 with an enhanced function (eg, *1/*17, *17/*17) can be referred to ultrafast metabolizers. The average polyethnic frequency of occurrence of the allele is ~ 3-21%. Some studies have shown that this allele leads to an increase in platelet inhibition and response to clopidogrel [20, 21] and, possibly, an increased risk of bleeding [22, 23]. However, other studies have not confirmed this effect of CYP2C19*17 [22- 28].

Contradictory results of studies are possibly associated with the nonequilibrium cohesion existing between alleles *17 and *2. The phenotypic consequences of the combination of the allele with loss of functions and the allele *17 that make up the heterozygous genotype (for example, *2/*17) are currently unclear, but the manifestations may be in the phenotypes of both fast and slow metabolizers, and apparently depend on specific substrate [29].

According to Li Y, Tang H.L. in comparison with CYP2C19*17 non-carriers, carriers of that gen had a 16% risk decrease of ACS recurrence in 9428 patients, receiving clopidogrel during 1 year, but they have observed increased bleeding risk. As expected, CYP2C19*17 carriers also have a lower level of residual platelet reactivity than the carriers. The clinical significance of the CYP2C19*17 variant (-806C> T in the promoter region of the gene, responsible for its enhanced function) has not been studied until its presence was associated with increased efficacy and bleeding risk in patients who received clopidogrel.

Although studies show, that CYP2C19*17 carriers have lower residual platelet activity during clopidogrel treatment in comparison with non-carriers [15, 16], a 22% reduction in recurrent ACS and a 37% reduction of need in revascularization (PCI or CABG) in patients with acute myocardial infarction [17], as well as a significantly lower risk of recurrent ischemic cardiovascular events [18], other studies do not support such increased efficiency [10, 12, 19]. Moreover, a correlation between CYP2C19*17 presence and fatal cardiovascular events [12] or stent thrombosis was not observed [3]. Some of the inconsistencies in CYP2C19*17 data may be associated with small sample size of studies, a difference in study design, the studied population heterogeneity, different methodologies for genotyping and testing platelet functions, and partial conjunction CYP2C19*17 with CYP2C19*2 [12, 18, 20-22].

In his basic study, Sim et al. [9] reported a low frequency of the CYP2C19*17 allele in Chinese population (4%) in comparison to the Ethiopians and Swedes, who had the same distribution (18% in both). This broad interethnic variation in the allele frequency has now been confirmed in several studies [8, 13-14, 16-17, 21, 23-27]. The allele prevalence was usually <5% in Asians and about four times higher in the white and African populations. The frequency of CYP2C19*17 alleles in the Iranian population is 21.6% and is similar to the Middle East countries or Europe. The high frequency of the CYP2C19*17 allele in the Iranian population underlines this new allele variant importance in the metabolism of CYP2C19 substrates [29].

Conclusion

Thus, a review of literature data has shown the need for a genetic study (CYP2C19 genotyping) responsible for the metabolism of clopidogrel in patients with ACS/PCA to improve their clinical outcome.

Despite a large number of studies showing a decrease in the effectiveness of clopidogrel in patients with ACS/PCA from different ethnic groups with CYP2C19 genetic polymorphism, the role of genetic factors in individuals of the Kazakh population remains unclear. The studies on identification of the status of metabolizers in individuals with risk of stents thrombosis early developing are few and contradictory in accessible national literature.

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