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GENETIC FEATURES OF ATRIAL FIBRILLATION ON THE BACKGROUND OF ARTERIAL HYPERTENSION

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Annotation.

Atrial fibrillation (AF) is the most common of persistent arrhythmias, especially in elderly patients. At a young age (under 50 years old) this arrhythmia occurs in 1 in 1000 people. Currently, AF is registered in 1 out of 25 people 60 years and older and in 1 out of 10 in the age group over 80 years [1]. Over the past 20 years, there has been a twofold increase in the incidence of AF among the male population, and the hospitalization of patients with AF has increased by 66%. The reasons for this increase are ambiguous and not completely clear, among the possible reasons are considered: an increase in the proportion of elderly people, improved diagnosis of AF at the outpatient stage, an increase in the number of survivors of acute myocardial infarction (MI), etc. [2]. It is important that the tendency to increase the frequency of AF does not disappear and, moreover, the tendency to progression increases.

Purpose – To study genetic determinants in patients with atrial fibrillation (AF) on the background of arterial hypertension (AH) in combination with various extracardiac comorbid pathology.

Material and methods – In a prospective cohort study included 167 patients with paroxysmal and persistent forms of AF and stage II hypertension without CAD. The average age of the patients studied was 53.3±7.1 years. DNA isolation from blood leukocytes was carried out by phenol-chloroform extraction. Testing polymorphism rs2200733, polymorphism 174G/C (174G/C (rs1800795) gene IL6), the IL6 gene performed with PCR with RFLP. Testing of statistical hypotheses was carried out at a critical level of significance p=0.05, i.e. the difference was considered statistically significant at $p<0.05$. The lower limit of the evidential power was taken equal to 80%.

Results – This study shows associations of polymorphisms 174G/C (rs1800795) of the IL6 gene, the IL6 gene and rs2200733 chromosome 4q25 with AF on the background of comorbidities: AH, chronic obstructive pulmonary disease, hypothyroidism, T2DM, abdominal obesity. Associations of polymorphism 174G/C (rs1800795) of the IL6 gene with the risk of recurrence of AF on the background of individual comorbidities were also found; polymorphism rs2200733 chromosome 4q25 with triglyceride levels, index atherogenicity, creatinine, fibrinogen, with the number of months before the development of relapse; 174G/C (rs1800795) of the IL6 gene – with HDL cholesterol levels, creatinine, diastolic blood pressure, galectin-3.

Conclusion – The results contributes to the study of such a complex phenomenon as the secondary form of atrial fibrillation, contributes to the accumulation of knowledge, bringing closer the time when therapeutic interventions will be individualized, based on an understanding of the pathological process in each patient.

Keywords: Atrial fibrillation, polymorphism, rs2200733, 174G/C (rs1800795) of the IL6 gene, IL6, extracardiac pathology

ARTERIAL GIPERTENZIYA FONIDA ATRIYAL FIBRILATSIYANING GENETIK XUSUSIYATLARI

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Annotatsiya.

Atriyal fibrilatsiya (AF) doimiy aritmiyalarning eng keng tarqalgani, ayniqsa keksa bemorlarda. Yoshligida (50 yoshdan kichik) bu aritmiya har 1000 kishidan bittasida uchraydi. Hozirgi vaqtda AF 60 va undan katta yoshdagi 25 kishidan 1 tasida va 80 yoshdan oshgan 10 kishidan 1 tasida qayd etilgan [1]. So'nggi 20 yil ichida erkaklar orasida AF bilan kasallanish darajasi ikki baravar oshdi, AF bilan kasallangan bemorlarni kasalxonaga yotqizish 66 foizga oshdi. Ushbu o'sishning sabablari noaniq va to'liq aniq emas, mumkin bo'lgan sabablar qatoriga quyidagilar kiradi: keksa yoshdagi odamlarning o'ziga xos vaznining ko'payishi, ambulatoriya bosqichida AF diagnostikasining yaxshilanishi, o'tkir miokard infarktidan (mi) omon qolganlar sonining ko'payishi va boshqalar. [2]. Muhimi shundaki, AF chastotasining o'sish tendentsiyasi yo'qolmaydi va bundan tashqari, rivojlanish tendentsiyasi ortadi.

Maqsad – Arterial gipertenziya (ah) fonida atriyal fibrilatsiyali (AF) bemorlarda genetik determinantlarni turli ekstrakardiyal komorbid patologiya bilan birgalikda o'rganish.

Material va usullar – Istiqbolli kohort tadqiqotiga AF ning paroksismal va doimiy shakllari va SAPRSIZ II bosqich gipertenziyasi bo'lgan 167 bemor kiritilgan. Tekshirilayotgan bemorlarning o'rtacha yoshi 53,3±7,1 yoshni tashkil etdi. Qon leykotsitlaridan DNKni ajratib olish fenol-xloroform ekstraktsiyasi usuli bilan amalga oshirildi. Rs2200733 polimorfizmini, il 6 genining 174g/C (174g/C (rs1800795) polimorfizmini, IL6 genini sinovdan o'tkazish PDRF bilan PCR yordamida amalga oshirildi. Statistik gipotezalarni tekshirish muhim ahamiyatga ega bo'lgan kritik darajada amalga oshirildi p \ u003d 0.05, ya'ni.farq p<0.05 da statistik ahamiyatga ega deb hisoblangan. Daliliy quvvatning pastki chegarasi 80% ga teng edi.

Natijalar – Ushbu tadqiqot il6 genining 174g/C (rs1800795) polimorfizmlari, 4Q25 xromosomasining IL6 geni va rs2200733 ning af bilan bog'liq kasalliklar fonida assotsiatsiyasini ko'rsatadi: ah, surunkali obstruktiv o'pka kasalligi, hipotiroidizm, II turdagi diabet, qorin bo'shlig'idagi semirish. Shuningdek, il6 genining 174g/C (rs1800795) polimorfizmining ayrim qo'shma kasalliklar fonida FP qaytalanish xavfi bilan assotsiatsiyalari aniqlandi; triglitseridlar darajasi, aterogenlik indeksi, kreatinin, fibrinogen bilan rs2200733 4q25 xromosomasining polimorfizmi, relaps rivojlanishidan bir necha oy oldin; IL6 genining 174G / C (rs1800795) – HDL, kreatinin, diastolik qon bosimi, galektin-3 XS darajasi bilan.

Xulosa – Tadqiqot atriyal fibrilatsiyaning ikkilamchi shakli kabi murakkab hodisani o'rganishga hissa qo'shadi, har bir bemorda patologik jarayonning xususiyatlarini tushunishga asoslangan terapevtik aralashuvlar individuallashtirilgan vaqtni yaqinlashtirib, bilimlarni to'plashga yordam beradi.

Kalit so'zlar: atriyal fibrilatsiya, polimorfizm, rs2200733, 174g/C (rs1800795) il6, IL6 genlari, ekstrakardiyal patologiya

ГЕНЕТИЧЕСКИЕ ОСОБЕНОСТИ ФИБРИЛЯЦИИ ПРЕДСЕРДИЙ НА ФОНЕ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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Аннотация.

Фибрилляция предсердий (ФП) – это наиболее распространённая из стойких аритмий, особенно у пациентов пожилого возраста. В молодом возрасте (моложе 50 лет) эта аритмия встречается у 1 на 1000 человек. В настоящее время ФП регистрируется у 1 из 25 человек 60 лет и старше и у 1 из 10 – в возрастной группе старше 80 лет [1]. За последние 20 лет отмечено двукратное увеличение частоты случаев ФП среди мужского населения, на 66% выросла госпитализация пациентов с ФП. Причины такого роста неоднозначны и не вполне ясны, среди возможных причин рассматриваются: увеличение удельного веса людей пожилого возраста, улучшение диагностики ФП на амбулаторном этапе, повышение числа выживших после острого инфаркта миокарда (ИМ) и др. [2]. Важно то, что тенденция к увеличению частоты ФП не исчезает и, более того, увеличивается склонность к прогрессированию.

Цель исследования – Изучить генетические детерминанты у больных с фибрилляцией предсердий (ФП) на фоне артериальной гипертензии (АГ) в сочетании с различной экстракардиальной коморбидной патологией.

Материал и методы – В проспективное когортное исследование включены 167 пациентов с пароксизмальной и персистирующей формами ФП и гипертонической болезнью II стадии без ИБС. Средний возраст исследуемых пациентов составил 53,3±7,1 года. Выделение ДНК из лейкоцитов крови проводилось методом фенол-хлороформной экстракции. Тестирование полиморфизма rs2200733, полиморфизма 174G/C (174G/C (rs1800795) гена IL6), гена IL6 выполнялось с помощью ПЦР с ПДРФ. Проверка статистических гипотез проводилась при критическом уровне значимости p=0,05, т.е. различие считалось статистически значимым при p<0,05. Нижняя граница доказательной мощности бралась равной 80%.

Результаты – В настоящем исследовании показаны ассоциации полиморфизмов 174G/C (rs1800795) гена IL6, гена IL6 и rs2200733 хромосомы 4q25 с ФП на фоне сопутствующих заболеваний: АГ, хроническая обструктивная болезнь лёгких, гипотиреоз, сахарный диабет II типа, абдоминальное ожирение. Обнаружены также ассоциации полиморфизма 174G/C (rs1800795) гена IL6 с риском рецидива ФП на фоне отдельных сопутствующих заболеваний; полиморфизма rs2200733 хромосомы 4q25 с уровнями триглицеридов, индекса атерогенности, креатинина, фибриногена, с количеством месяцев до развития рецидива; 174G/C (rs1800795) гена IL6 – с уровнями ХС ЛПВП, креатинина, диастолического АД, галектин-3.

Заключение – Исследование вносит свой вклад в изучение такого сложного феномена, как вторичная форма фибрилляции предсердий, способствует накоплению знаний, приближая то время, когда терапевтические вмешательства будут индивидуализированными, основанными на понимании особенностей патологического процесса у каждого пациента.

Ключевые слова: фибрилляция предсердий, полиморфизм, rs2200733, 174G/C (rs1800795) гена IL6, IL6, экстракардиальная патология

Introduction. Atrial fibrillation (AF) is the most common of persistent arrhythmias, especially in elderly patients. At a young age (under 50 years old) this arrhythmia occurs in 1 in 1000 people. Currently, the FP is registered with 1 in 25 people are 60 years old and older, and 1 in 10 are in the age group over 80 years old [1]. Over the past 20 years, there has been a twofold increase in the incidence of AF among the male population, and the hospitalization of patients with AF has increased by 66%. The reasons for this increase are ambiguous and not entirely clear, among the possible reasons are considered: an increase in the proportion of elderly people, improved diagnosis of AF at the outpatient stage, an increase in the number of survivors of acute myocardial infarction (MI), etc. [2]. The important thing is that the tendency to increase the frequency AF does not disappear and, moreover, the tendency to progression increases. The term "progression of AF" refers to the process of steady development of the paroxysmal form AF in the direction of chronic form [3]. It is estimated that 2.2 million residents of the United States had paroxysmal or persistent forms of AF, which within 5 years turned into chronic 67% of patients. In Europe, which has a population of about 513 million people, 8.2 million patients with AF have been registered, the risk of AF progression is 1:4 for men and women aged 40 years and older. It is predicted that the number of people with this arrhythmia in the United States will increase from 2.5 million in the early 2000s to 15 million in 2050 [4]. This gave rise to calling such a process an "epidemic", and the effect of it a "time bomb".

To date, there are many clinical studies devoted to the study of risk factors for AF, including the main factor – arterial hypertension (AH), which contributes to ventricular hypertrophy and atrial dystrophy. However, insufficient attention is paid to the progression of AF [5]. Abdominal obesity (AO) is a frequent risk factor for hypertension and contributes to structural and functional rearrangements of the myocardium, known as the "lipotoxicity phenomenon". Lipotoxicity involves the accumulation of plasma triglycerides in the myocar-

dium and leads to myocardial steatosis. Thus, with obesity, dilatation of the heart cavities is formed. Consequently, both hypertension and AO contribute to myocardial dysfunction, the development of electrical instability and the appearance of AF, and, with irrational management of patients, progression to a chronic form [6].

With new discoveries in the field of genetics, the occurrence of the idiopathic form of AF becomes less and less every time. Most often, genetic AF is autosomal dominant due to impaired functioning of various potassium channels in phase 3. Less often, AF can be autosomal recessive or sex-linked - with damage to sodium channels.

There are also known forms of AF with mutations in many genes – familial polygenic atrial fibrillation [7].

Hereditary AF can be an independent nosological unit or accompany such channelopathies as prolonged or shortened QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia. In addition, AF may be associated with such structural genetic cardiomyopathies as familial dilated cardiomyopathy, hypertrophic cardiomyopathy, idiopathic restrictive cardiomyopathy, arrhythmogenic right ventricular dysplasia, as well as unclassified diseases (non-compact cardiomyopathy, fibroelastosis) [8].

The association of polymorphisms with blood pressure was first shown by Newton-Cheh C et al in 2009 when analyzing the results of a large international study GWAS [9, 10]. In 2010, it was confirmed in Korea [11, 12]. However, due to the fact that there are significant geographical differences in the allelic frequencies of ONP associated with CVD, studies in ethnic groups are required to confirm previously discovered associations [13-16]. In seven studies of hypertension (16368 cases/19707 controls) performed in In East Asia, they did not find a significant association with hypertension.

Research materials and methods. The prospective cohort study included 161 patients. Inclusion criteria: age 45-65 years, stage III hypertension

(ESH/ESC, 2018), atrial fibrillation, paroxysmal or persistent form (RCT, VEA and ASX, Moscow, 2017) and one of the following diseases: type II diabetes mellitus (WASD/ESC, 2017), subclinical hypothyroidism (ETA, 2013), abdominal obesity (AACE/ACE, 2014), chronic obstructive pulmonary disease (ERS, 2017). According to the definition of the expert consensus document (HRS/EHRA/ ECAS, 2012), the term "progression of AF" refers to the process of steady development of the paroxysmal form of AF towards the chronic form.

Clinical, anthropometric and laboratory parameters, results of instrumental diagnostics were evaluated: ECG; XM ECG, SMAD using the SCHILLER daily monitoring system (Schiller, Switzerland), echocardiography in M and 2D modes on the Vivid 7 device (General Electric, USA). The level of galectin-3 was determined in blood serum by enzyme immunoassay using the Human Galectin-3 ELISA kit; eBioscience" (Bender MedSystems GmbH, Austria), the minimum concentration of determination is 0.12 ng/ml. The concentration of NT-proBNP was determined using a set of reagents "NTproBNP – ELISA – Best". CRP (C-reactive protein) was determined by ELISA using the ELISA test system (Biomerica, USA). DNA extraction from blood leukocytes was carried out by phenol-chloroform extraction [Smith K., 1990]. RS2200733 polymorphism testing, polymorphism - 174G/C (174G/C (rs1800795) of the IL6 gene) of the IL6 gene was performed using PCR with PDRF according to previously published methods.

Statistical analysis. Empirical data distributions were tested for compliance with the law of normal distribution according to the Shapiro-Vilka and Kolmogorov-Smirnov criteria. Due to the small number of indicators corresponding to the normal distribution in the studied groups, nonparametric Mann-Whitney and Kruskal-Wallis criteria were used for comparison. The "Proportional Cox Model" was used, a method of multiple regression with the determination of the value of the risk ratio and its confidence interval. The exact two-sided Fisher criterion was used to compare binary and categorical indica-

tors. Statistical hypotheses were tested at a critical significance level of p=0.05, i.e. the difference was considered statistically significant if p<0.05. The lower limit of the evidence capacity was assumed to be 80%.

The results and their discussion. At the first stage, the analysis of the frequencies of genotypes and alleles of the rs2200733 polymorphism of chromosome 4q25 was performed in groups of patients with various concomitant diseases: atrial fibrillation in patients with arterial hypertension ((AH/AF), AF in patients with AH and chronic obstructive pulmonary disease (COPD), AF in patients with AH and hypothyroidism (G), AF in patients with hypertension and type II diabetes mellitus (DM), AF in patients with hypertension and abdominal obesity (AO).

Significant differences in the frequencies of rs2200733 genotypes were obtained chromosomes 4q25 between groups with AH and AO (p=0.006). The ratio of the chances of detecting a carrier of the CT genotype in the group with AO is 4.8 times less than in the group with only AH (18.2% vs 51.4; 95% CI 1.6-14.2). There are also differences in the frequencies of rs2200733 chromosome 4q25 genotypes between groups with AO and COPD (OR=4.5; 95% CI 1.4-14.0; p=0.015). The frequency of the T allele was lowest in the AO group (9.1%) and highest in the COPD group (28.3%), with statistically significant differences of p=0.006. The frequencies of alleles also differ between groups with AO and with AH (p=0.014).

When comparing the frequencies of genotypes and alleles of rs2200733 chromosome 4q25 in patients with and without AF recurrence, no significant differences were found. When analyzing the genotype frequencies of the rs2200733 polymorphism of chromosome 4q25 in patient groups with AF on the background of various concomitant diseases with relapse. Even without it, their significant fluctuations were revealed. The frequency of the CC genotype was higher in the groups of patients with relapse AF compared with patients

without relapse on the background of diabetes and COPD and, conversely, lower on the background of hypothyroidism and hypertension.

Statistically significant differences in triglyceride levels, atherogenicity index, creatinine, fibrinogen levels, and the number of months before relapse were obtained. Index atherogenicity and creatinine levels were higher in carriers of the CT genotype compared with carriers of the CC genotype, whereas the levels of triglycerides, fibrinogen and the duration of the time interval before relapse were higher in carriers of the CC genotype compared with carriers of the CT genotype. The available literature does not describe differences in the level of the above indicators between carriers of different genotypes rs2200733 chromosomes 4q25 [17-19] except for the duration of the time interval before the recurrence of AF. Parvez In et al (2013) [20] found that AF recurrence after cardioversion occurs faster in carriers of the T allele, and in a dose-dependent manner: TT homozygotes – 7 days (interquartile range 4-56 days); CT heterozygotes – 54 days (28-135) and CC homozygotes – 64 days (29-180), p=0.03. That is, the data obtained on a group of patients with AF in Novosibirsk, they coincide with the results of other authors [20, 21].

The association of rs2200733 chromosome 4q25 with AF was shown in four independent cohorts [22]. However, later in Poland, no association of this polymorphism was found in the case of isolated AF in persons under 40 years of age [23], and in the USA they found: OR 1.62 (95% CI, 1.16-2.27; p=0.004) [24]. In a meta-analysis published in 2013 (10546 patients with AF and 72789 people in control), the odds ratio of AF associated with rs2200733 chromosome 4q25 is 1.89 (95% CI 1.62-2.16; p<0.001) [25]. The biological basis of the electrical instability of the heart caused by this non-coding variant is unknown. However, a detailed ECG analysis revealed that there is an association between the rs2200733 genotypes of chromosome 4q25 and the duration of the PR interval [26]. In the media group TT the average PR interval was 189.5±35.8 ms compared with the average PR intervals of 172.0±29.0 and 171.0±27.1 ms for

the CT and CC groups, respectively (p=0.013 and p=0.006) [27]. In addition, other researchers have shown the effect of rs2200733 of chromosome 4q25 on the clinical expression of rare mutations of cardiac ion channels associated with familial AF. On this basis, they formulated a hypothesis about the complex genetic architecture of AF, which includes both rare and common genetic variants [28]. And according to the data Lahtinen AM et al (2012) increased the risk of sudden cardiac death in carriers of the allele T. The effectiveness of catheter ablation for the treatment of AF is also associated with rs2200733. The authors even believe that the polymorphism rs2200733 Chromosome 4q25 may be promising as an objective marker that can be used as a clinical tool for selecting patients for treatment AF by catheter ablation [24].

Significant differences in the frequencies of 174G/C genotypes were obtained (rs1800795) of the IL6 gene between groups with DM and AH (p=0.047). The odds ratio of detecting a carrier of the CC genotype in the group with DM is significantly lower compared to the group with AH (5.6% vs 27.0%; p=0.024). There are also differences in the frequency of the CC 174G/C genotype (rs1800795) of the IL6 gene between groups with DM and hypothyroidism (p=0.025), with DM and AO (p=0.020). There was no significant increase in the frequency of the C allele in the COPD group. Although Volchkova EA et al. (2015), testing the hypothesis that the development of AF in patients with COPD is directly related to the inflammatory system, found an association with 174G/C (rs1800795) of the IL6 gene. The factors associated with AF were: the volume of the left atrium (p=0.027), the volume of the right atrium (p=0.021) and the carriage of the C allele of the polymorphic marker G (-174) C of the IL6 gene (p=0.003) [7].

When comparing the frequencies of genotypes and alleles 174G/C (rs1800795) no significant differences were found in IL6 gene in patients with and without AF recurrence. Perhaps this is dueto the relatively small size of the study group. Previously, a number of authors have shown the association of

polymorphisms rs2200733 chromosomes 4q25 and 174G/C (rs1800795) of the IL6 gene with postoperative atrial fibrillation. IL6 protein is produced by endothelial cells, vascular smooth muscle cells, and myocytes in ischemia. Its level is associated with AF in coronary disease, after cardiac surgery, cardioversion and catheter ablation [24, 25].

When analyzing the frequencies of 174G/C polymorphism genotypes (rs1800795) of the IL6 gene in groups of patients with AF against the background of various concomitant diseases with and without AF recurrence, their significant fluctuations were found: the frequency of the CC genotype was significantly higher in patients with AF recurrence in the groups with hypothyroidism and hypertension, in the group with COPD – significantly lower, and in the group with DM it was the same in patients with and without a recurrence of AF. In the group with hypothyroidism, AF recurrence was significantly less frequent in carriers of the CG genotype, p=0.030.

Some patients had cardioembolism within a year after inpatient treatment. When comparing the frequencies of the 174G/C (rs1800795) IL6 gene genotypes in patients with and without cardioembolism, significant differences were obtained in the form of an increase in the frequency of carriage of the heterozygous genotype CG in patients with cardioembolism (HR=2.25; 95% CI 1.01-5.04, p=0.05).

When comparing the level of the studied indicators in carriers of the CC genotype with the combined group of carriers of the CG and GG genotypes, a statistically significant difference in differences remains. Carriers of the CC genotype had significantly higher galectin-3 levels than carriers of the other two genotypes, p=0.022.

The secondary form of atrial fibrillation, as a multifactorial disease, develops under the influence of many factors, both environmental and hereditary. The complexity of the etiopathogenesis of the disease poses an extremely difficult task for researchers to find factors that play a leading role in the devel-

opment of the pathological process. Currently, associative studies of atrial fibrillation with polymorphisms of more than 260 genes have been conducted, and genome-wide associative studies have been performed. The reproducibility of the results depends on a number of factors: age, gender, concomitant diseases, ethnicity, penetrance, expressiveness, pleiotropy, various epigenetic influences, etc. [24, 25]. Nevertheless, each new study contributes to the study of such a complex phenomenon as the secondary form of atrial fibrillation, contributes to the accumulation of knowledge, bringing closer the time when therapeutic interventions will be individualized, based on an understanding of the features of the pathological process in each patient.

As a result of this study, polymorphism rs1378942 of the CSK gene, rs2200733 of chromosome 4q25, 174G/C (174G/C (rs1800795) of the IL 6 gene), IL6 gene was detected and associations with a number of indicators that have a prognostic role in the development and progression of atrial fibrillation in patients with hypertension in combination with certain extracardial diseases: sugar diabetes, chronic obstructive pulmonary disease, hypothyroidism and abdominal obesity.

Conclusions/Conclusion. As a result of the study, associations of polymorphisms 174G/C (rs1800795) of the IL6 gene were established and rs2200733 chromosomes 4q25 with atrial fibrillation on the background of concomitant diseases: arterial hypertension, chronic obstructive pulmonary disease, hypothyroidism, type II diabetes mellitus, abdominal obesity. The associations of IL6 gene polymorphism 174G/C (rs1800795) with the risk of recurrence of atrial fibrillation against the background of diabetes mellitus, chronic obstructive pulmonary disease and abdominal obesity were determined. Associations were found: rs2200733 of chromosome 4q25 with levels of triglycerides, creatinine, fibrinogen, with sinus rhythm duration and atherogenicity index, and 174G/C (rs1800795) of the IL6 gene with levels of HDL cholesterol, creatinine, diastolic blood pressure, galectin-3.

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