Результаты исследования ассоциации полиморфного локуса rs11212617 гена *ATM* с ответом на терапию метформином у больных сахарным диабетом 2-го типа

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Обоснование. В последние годы активно изучаются генетические аспекты, влияющие на эффективность терапии метформином (МФ) у больных сахарным диабетом 2-го типа (СД2).

Цель. Изучить ассоциацию полиморфного локуса rs11212617 гена *ATM* с ответом на терапию МФ у больных СД2 в Новосибирской области и провести метаанализ ранее опубликованных данных.

Материал и методы. Проведено одномоментное поперечное обследование 460 больных СД2 (97 мужчин и 363 женщины), получавших МФ как в монотерапии, так и в сочетании с препаратами сульфонилмочевины (СМ). В зависимости от уровня HbA_{1c} пациенты были распределены на группы: 209 больных, имеющих целевой HbA_{1c} на фоне терапии МФ, и 251 больной, не достигшие целевого уровня HbA_{1c} на максимальной дозе МФ. Определение аллелей и генотипов проводили с помощью ПЦР в режиме реального времени, с использованием TaqMan-зондов в Институте химической биологии и фундаментальной медицины СО РАН.

Результаты. Частота редкого аллеля С полиморфного локуса rs11212617 гена *ATM* у обследованных лиц составила 0,41 и статистически не различалась между подгруппами монотерапии МФ и комбинированной терапии. Не выявлено статистически значимой ассоциации генотипа полиморфного локуса rs11212617 гена *ATM* с типом ответа как в общей группе пациентов (OR=0,94; 95% CI 0,73—1,23; p=0,67), так и в подгруппах монотерапии МФ (OR=0,90; 95% CI 0,65—1,25; p=0,54) и комбинированной терапии (OR=1,02; 95% CI 0,72—1,43; p=0,92). Однако результаты метаанализа подтверждают ассоциацию аллеля С с достижением целевого уровня HbA_{1c} (суммарный OR=1,27; 95% CI 1,10—1,46; p=0,0008).

Заключение. Полиморфный локус rs11212617 гена *ATM* может влиять на эффективность терапии МФ у пациентов с СД2.

Ключевые слова: сахарный диабет 2-го типа, метформин, ATM (rs11212617).

Results of studying the association between the rs11212617 polymorphism in the *ATM* gene and response to metformin therapy in patients with type 2 diabetes mellitus

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Rationale. The genetic aspects influencing the effectiveness of metformin (MF) therapy in patients with type 2 diabetes mellitus (DMT2) have recently been intensively studied.

Objective — to study the association between the rs11212617 polymorphism in the *ATM* gene and response to metformin therapy in DMT2 patients in the Novosibirsk region and to conduct a metaanalysis of the previously reported data.

Material and methods. 460 DMT2 patients (97 males and 363 females) who received MF, both as a part of monotherapy and in combination with sulfonylurea (SU) drugs, were subjected to cross-sectional examination. Depending on HbA1c level, patients were divided into the following groups: patients who have attained the target HbA_{1c} level after MF therapy (n=209) and those who did not attain the target HbA_{1c} level although receiving the maximum dose of MF (n=251). Alleles and genotypes were determined by real-time PCR using TaqMan probes at the Institute of Chemical Biology and Fundamental Medicine (SB RAS).

Results. Frequency of the rare C allele of the rs11212617 polymorphism in the *ATM* gene in the examined patients was 0.41 and statistically did not differ between the subgroups who received MF monotherapy and combination therapy. Statistically significant association between the genotype of the rs11212617 polymorphism in the *ATM* gene and the type of response was revealed neither in the total group of patients (OR=0.94, 95% CI 0.73—1.23; p=0.67) nor in the MF monotherapy (OR=0.94, 95% CI 0.73—1.23; p=0.67) or combination therapy subgroups (OR=1.02, 95% CI 0.72—1.43; p=0.92). However, the metaanalysis results verify that the C allele is associated with attainment of the target HbA_{c1} level (the total OR=1.27, 95% CI 1.10—1.46; p=0.0008).

Conclusions. The rs11212617 polymorphism in the *ATM* gene can influence the effectiveness of MF therapy in DMT2 patients.

Keywords: type 2 diabetes mellitus, metformin, ATM (rs11212617).

BACKGROUND

Currently, metformin (MF) is the first-line medication in the treatment of type 2 diabetes mellitus (T2DM) [1, 2]. It is known that the effectiveness of MF therapy may vary among T2DM patients. This variability may be due to psychological and social factors, malabsorption of the drug from the gastrointestinal tract, changes in metabolism, distribution and excretion, which in turn de-

pend on renal function, enzyme systems activity, and drug interactions, leading to alteration of MF pharmacokinetics and pharmacodynamics. MF is used in clinical medicine for more than 50 years. However, the mechanisms underlying its therapeutic effects are not fully understood. After entering the cell, MF is accumulated in the mitochondrial matrix. Mitochondrial respiratory chain complex I is a key target of MF, whose inhibition results is decreased production of ATP and increased levels of AMP and ADP. This change in cellular energy metabolism is detected by AMP-activated protein kinase (AMPK), the main cellular energy sensor. MF enhances phosphorylation processes, which leads to increased cellular level of AMPK followed by with inhibition of mTOR (mammalian target of rapamycin) protein kinase, which affects metabolism and growth factor signaling, differentiation, aging, apoptosis, and autophagic processes [3, 4]. Activation of AMPK reduces activity of cell cycle enzymes, gluconeogenesis, and glycogenolysis; stimulates anaerobic glycolysis, fatty acid oxidation in liver, and ketogenesis; inhibits lipogenesis, synthesis of cholesterol and triglycerides, inhibits lipolysis and lipogenesis in adipocytes; stimulates fatty acid oxidation and glucose uptake in skeletal muscles through enhanced biosynthesis of GLUT-1 and GLUT-4 glucose transporters; modulates insulin secretion by beta cells [5]. It is assumed that decreased expression and activity of AMPK is associated with obesity, metabolic syndrome, disturbance of carbohydrate metabolism, cancer, and myocardial ischemia [2, 5]. In recent years, genetic aspects affecting the efficacy of MF therapy are being extensively studied. The study of the effect of MF on AMPK, the product of ataxia-telangiectasia (*ATM*) gene expression, is of greatest interest [6]. According to the literature, the minor C allele at the polymorphic locus rs11212617 in the *ATM* gene is associated with good response to MF [7].

AIM

The study was aimed at assessing association of the polymorphic locus rs11212617 in the *ATM* gene with the response to MF therapy in T2DM patients in the Novosibirsk region and conducting metaanalysis of previously published data.

METHODS

Study Design

A single-step cross-sectional survey of 2000 T2DM patients (450 males and 1550 females) was carried out on the basis of the mobile diabetes center (Diamobil) in the Novosibirsk region.

Inclusion criteria

A total of 2000 patients were examined and 460 of them were included in the study (97 males and 363 fe-

males), who received MF either as monotherapy or in combination with sulfonylurea (SU) medications. Exclusion criteria were as follows: type 1 diabetes mellitus (T1DM), other types of diabetes, T2DM with insulin therapy, cancer, NYHA III—IV heart failure, hepatic insufficiency (more than 7 points on the Child-Pugh scale), decreased glomerular filtration rate (GFR) of less than 45 mL/min × 1.73 m², treatment with corticosteroids or estrogens, alcoholism, drug addiction, dementia, or severe mental disorders.

Study conditions

The study included only patients, who provided written informed consent.

Duration of the study

From 2012 to 2015.

Description of medical intervention

All 460 patients underwent complete clinical examination; the level of glycated hemoglobin (HbA_{1c}) was assessed using immuno-turbidimetric method on BIO-RAD D10 analyzer (US). DNA isolation and genotyping of rs11212617 polymorphic locus of the *ATM* gene was carried out in the laboratory of Pharmacogenomics at the Institute of Chemical Biology and Fundamental Medicine, Siberian Branch of the Russian Academy of Sciences (SB RAS) using TaqMan real-time PCR. PCR was performed in a final volume of 25 μl, containing 65 mM Tris-HCl (pH 8.9), 24 mM ammonium sulfate; 3.5 mM $MgCl_2$; 0,05% Tween-20; 300 nM of each primer; 100 nM of each Taq Man-probe conjugated to FAM or R6G; 200 μM of dNTP, 20—100 ng of DNA, and 1 activity unit of Taq-DNA polymerase. Amplification was carried out using CFX384 amplifier (Bio-Rad, USA) under the following conditions: initial 3' denaturation at 96 °C followed by 50 cycles, including denaturation at 96°C during 8 sec, primer annealing and subsequent elongation at T_{ann} = 60 °C for 40 seconds (each step was followed by registration of the fluorescence signal in the range corresponding to fluorescence intervals of FAM and R6G fluorophores). Genotype of the polymorphic locus rs11212617 was determined using the following oligonucleotides: forward primer 5'-GATCTACATATACCAAT-TACAAAGG-3', reverse primer 5'-GGATAA-CATATAGTTGGGTCTTG-3', probe for A allele 5'-FAM-CAGAGAATGTCAGAGCGG-BHQ-3', probe for C allele 5'-R6G-CAGAGACTGTCAGAGC-GG-BHQ-3'.

The main result of the study

Association of the polymorphic locus rs11212617 in the *ATM* gene with the response to MF therapy in T2DM patients in the Novosibirsk region was evaluated based on HbA_{1c} level. Patients who have attained target HbA_{1c} values in accordance with the algorithms of specialized medical care for diabetic patients (2015) were included in

Table 1. Clinical and laboratory characteristics of the examined patients

Parameter	Group with good response to MF, n=209	Group with poor response to MF, n=251	p
Sex, male/female	29/128	17/68	
Age, years	60.4±8.9	57.5±8.1*	0.0002
DM duration, years	5.1±5.1	7.2±6.0*	0.00005
Age of DM onset, years	55.4±9.6	50.2±8.6*	<0.00001
BMI, kg/m²	35.2±6.2	34.2±7.1	0.21
HbA_{1c}, %	6.7±0.4	9.8±1.6*	<0.00001
HOMA-IR	3.4±2.2	3.5±2.7	0.93
GFR, ml/min × 1,73 m²	73.8±11.4	75.4±14.7	0.37
ALT, units/l	27.8±22.7	29.8±20.8	0.52
AST, units/l	26.7±12.9	26.5±11.5	0.90

the group with good response to MF. Patients who have not attained target HbA_{1c} values were included in the group with poor response to MF.

Subgroup analysis

Depending on the level of HbA_{1c}, patients were divided into groups: patients with target HbA1c level during MF therapy (the group with good response to MF administered both as monotherapy and in combination with SU medications) and the group of patients who have not attained the target HbA_{1c} level, while receiving the maximum dose of MF.

Ethical review

Research protocol was approved by the ethics committee of the Novosibirsk State Medical University (Protocol No 52 of 19.03.13). All patients signed an informed consent before entering the study.

Statistical analysis

We used standard descriptive and comparative analysis. In the case of normal distribution, the data were represented as a mean value (M) and standard deviation (SD), in the case of asymmetric distribution, the data were represented as a median (Me) with 25 and 75 percentiles (25; 75). Pearson's χ^2 test was used to compare the frequency of alleles between the groups. Depending on the type of data distribution, analysis of variance (ANOVA) or Kruskal—Wallis test was used to evaluate the differences between the groups. The critical significance level was set at 0.05. Compliance with Hardy—Weinberg equilibrium was assessed using Fisher's exact test. Statistical analysis was performed using Genetics statistical package as implemented in R-project software (www.r-project.org) and Statistica 6.0 program. Metaanalysis, evaluation of the «archival box» effect (publication bias), and construction of «forest plots» and «funnel plots» were carried out using meta and rmeta packages as implemented in R-project software (www.r-project.org). PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) was searched for articles published up to and including May 12, 2016 using various combinations of «rs11212617», «T2DM», and «dia-

betes mellitus» keywords. Inclusion criteria were as follows: 1) the design of the study «case-control», 2) evaluation of the association of rs11212617 with attainment of target HbA_{1c} level of <7%, 3) presentation of the results in English, 4) availability of all information required to calculate OR. Metaanalysis included the results of two studies, Zhou [8, 11] and van Leeuwen [9], along with our results. We did not include the findings of Zhou (2014, RS11212617 is associated with metformin treatment response in type 2 diabetes in Shanghai local Chinese population) obtained for Chinese population, since the article is not available and the summary does not contain the required information. A total of 5494 T2DM patients, who received MF, were included in metaanalysis.

RESULTS

Objects (participants) of the study

The average age of the examined patients was 58.8±8.6 years, duration of T2DM — 6.2±5.7 years, HbA_{1c} level — 8.4±1.9%, BMI — 34.8±6.7 kg/m². The patients were divided into groups depending on HbA_{1c} level: the group with target HbA_{1c} level during MF therapy (the group with good response to MF (n=209), of whom 110 patients received MF monotherapy and 99 patients received a combination of the MF with SU; and the group of patients, who have not attained target HbA_{1c} level, while receiving the maximum dose of MF (the group with poor response to MF (n=251), of whom 58 patients received MF monotherapy and 193 patients received a combination of MF with SU.

The analysis of clinical data showed that patients in the group with poor response to MF were younger as compared to the group with good response to MF (57.5±8.1 vs. 60.4±8.9 years; p<0.05), had longer duration of the disease (7.2±6.0 vs. 5.1±5.1 years; p<0.05), higher HbA_{1c} levels (9.8±1.6% vs. 6.7±0.4%; p<0.05), earlier onset of the disease (50.2±8.6 vs. 55.4±9.6 years; p<0.05) and did not differ significantly in BMI, degree of insulin resistance, glomerular filtration rate (GFR), and transaminase levels **(Table 1)**.
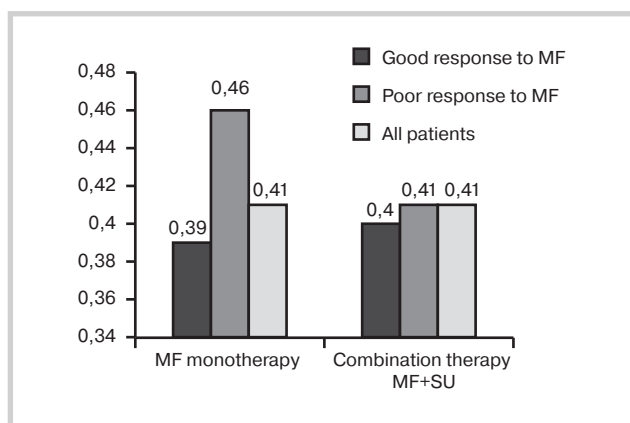
Figure 1. **Frequency of minor C allele at the rs11212617 polymorphic locus in the *ATM* gene in the groups with different responses to metformin therapy.**

Key findings

The distribution of genotypes of polymorphic locus rs11212617 in the *ATM* gene demonstrated no statistical deviations from Hardy-Weinberg equilibrium (p=0.21). In the examined patients, the frequency of the minor C allele at the polymorphic locus rs11212617 in the *ATM* gene was 0.41; in the subgroup of patients with poor response to MF monotherapy, it reached 0.46, and in the subgroup with good response it was 0.39 (p>0.05); in the overall group of patients with poor response to MF in combination with SU, the frequency of C allele was the same, 0.4 and 0.41, respectively and did not differ significantly from that in the group with good response **(Figure 1)**.

Logistic regression analysis of the relationship between the attainment of target HbA_{1c} level of <7% during MF treatment and genotypes of the polymorphic locus rs11212617 in the *ATM* gene demonstrated no statistically significant association of rs11212617 genotype with the type of response both in the overall group of patients (OR=0.94, 95% CI 0.73—1.23; p=0.67) and in subgroups of patients, who received MF monotherapy (OR=0.90, 95% CI 0.65—1.25; p=0.54) and combination therapy (OR=1.02, 95% CI 0.72—1.43; p = 0.92) **(Table 2)**.

Additional findings

We carried out meta-analysis of the results of our investigation and previously published studies. This meta-

analysis included a total of 5494 T2DM patients, who received MF **(Table 3)**.

According to the results of meta-analysis, minor C allele is a factor associated with good response to MF therapy (overall OR=1.27, 95% CI 1.10—1.46;p=0.0008, the level of heterogeneity p=0.02, the random effects model). We found no bias in the results published by other researchers, as shown by the correlation analysis (Begg's correlation analysis: z = −0.45; p=0.65) and regression test (Egger's test: t=−0.470; p=0.66). In addition, we carried out metaanalysis in both of the MF monotherapy and combination therapy subgroups. However, while the results in the MF monotherapy subgroup were similar [overall OR = 1.26, 95% CI 1.12—1.42; p=0.0001, the level of heterogeneity p=0.15, fixed-effects model, Begg's correlation analysis (z=1.32 and p=0.19), Egger's test (t=0.79; p=0.48), no impact of the polymorphic locus on the attainment of target HbA_{1c} level was observed in the group with combination therapy: overall OR=1.13, 95% CI 0.98—1.29; p=0.09, the level of heterogeneity p=0.75, fixed-effects model, Begg's correlation analysis (z=−0.56 and p=0.57), Egger's test 0.73). The results of metaanalysis and bias analysis of publications are plotted in **Figure 2**.

Adverse events

No adverse events were registered during this study.

DISCUSSION

The first pharmacogenetic genome-wide associative study of MF was carried out in Scotland in 1024 T2DM patients involved in the GoDARTS (Genetics of Diabetes Audit and Research Tayside) study [8]. Efficacy of MF therapy was assessed based on HbA_{1c} levels during the first 18 months from the start of therapy. The target HbA_{1c} level was <7%, which was considered as an evidence of the effectiveness of hypoglycemic therapy. The statistical analysis considered the initial level of HbA_{1c}, its dynamics during MF therapy, and creatinine clearance. Researchers have identified 14 polymorphisms in the region, comprising *ATM* gene. It was found that the carriers of minor C allele at the polymorphic locus rs11212617 in the *ATM* gene attained target HbA_{1c} level more frequently (OR= 1.64, 95% CI 1.37—1.99; p=1.9

Table 2. **Logistic regression analysis of the relationship between the attainment of target HbA_{1c} level of <7% during metformin therapy and genotypes of polymorphic locus rs11212617 in the *ATM* gene**

| | rs11212617 genotype in the ATM gene | | | OR (95% CI) | *p* |
	AA	AC	CC		
All examined patients	168 (0.37)	209 (0.45)	83 (0.18)	—	—
Patients with poor response to MF	87 (0.35)	121 (0.48)	43 (0.17)	—	—
Patients with good response to MF	81 (0.39)	88 (0.42)	40 (0.19)	0.94 (0.73—1.23)	0.67
MF monotherapy	45 (0.41)	44 (0.40)	21 (0.19)	0.90 (0.65—1.25)	0.54
combination therapy	36 (0.36)	44 (0.44)	19 (0.19)	1.02 (0.72—1.43)	0.92

Additive inheritance model was used to calculate OR for C allele in each cohort. The following parameters were added to the regression: patient sex, age at the time of the survey, daily dose of MF, and the creatinine level.

Table 3. Metaanalysis of the studies of the relationship between the attainment of target HbA$_{1c}$ level of <7% during MF therapy and the genotype of polymorphic locus rs11212617 in the *ATM* gene

Study	Number of patients	OR (95% CI)	*p*
Overall group			
GoDARTS (Discovery) [11]	1024	1.64 (1.37—1.99)	1.9×10^{-7}
GoDARTS (Replication) [11]	1783	1.21 (1.05—1.38)	0.007
UKPDS [11]	1113	1.37 (1.1—1.72)	0.006
Metaanalysis [GoDARTS (Discovery)+GoDARTS (Replication)+UKPDS] [11]	3920	1.35 (1.22—1.49)	2.9×10^{-7}
DCS [15]	929	1.27 (1.03—1.58)	0.028
Rotterdam Study [15]	182	1.44 (0.87—2.39)	0.15
CARDS [15]	254	1.03 (0.68—1.57)	0.86
Metaanalysis (DCS + Rotterdam Study + CARDS) [15]	1365	1.24 (1.04—1.49)	0.016
Metaanalysis [GoDARTS (Replication)+ UKPDS+DCS+RotterdamStudy+CARDS] [15]	4443	1.25 (1.13—1.38)	7.8×10^{-6}
Russia (our own data)	209	0.94 (0.73—1.23)	0.67
Metaanalysis [GoDARTS (Discovery) + GoDARTS (Replication) + UKPDS + DCS + Rotterdam Study + CARDS]+ Russia (our own data)	5494	1.27 (1.10—1.46)	0.0008
MF monotherapy			
GoDARTS (Replication) [8]	1460	1.25 (1.07—1.46)	0.005
UKPDS [8]	284	1.82 (1.20—2.78)	0.005
DCS [9]	547	1.32 (0.99—1.78)	0.062
Rotterdam Study [9]	65	1.97 (0.72—5.42)	0.19
CARDS [10]	81	1.50 (0.76—2.95)	0.23
Metaanalysis (DCS + Rotterdam Study + CARDS) [10]	693	1.38 (1.07—1.80)	0.015
Metaanalysis [GoDARTS (Replication) + UKPDS + DCS + Rotterdam Study + CARDS] [10]	2437	1.33 (1.16—1.50)	1.4×10^{-5}
Russia (our own data)	110	0.90 (0.65—1.25)	0.54
Metaanalysis [GoDARTS (Replication) + UKPDS + DCS + Rotterdam Study + CARDS]+ Russia	2547	1.26 (1.12—1.42)	0.0001
Combination therapy (MF + SU)			
GoDARTS (Replication) [8]	505	1.08 (0.84—1.40)	0.54
UKPDS [8]	829	1.23 (0.94—1.62)	0.13
DCS [9]	382	1.20 (0.87—1.66)	0.26
Rotterdam Study [9]	117	1.40 (0.77—2.57)	0.27
CARDS [10]	173	0.82 (0.46—1.46)	0.51
Metaanalysis (DCS + Rotterdam Study + CARDS) [10]	672	1.15 (0.89—1.48)	0.29
Metaanalysis [GoDARTS (Replication) + UKPDS + DCS + Rotterdam Study + CARDS] [10]	2006	1.15 (0.99—1.34)	0.067
Russia (our own data)	99	1.02 [0.72—1.43]	0.92
Metaanalysis [GoDARTS (Replication) + UKPDS + DCS + RotterdamStudy + CARDS]+ Russia (our own data)	2105	1.13 (0.98—1.29)	0.09

$\times 10^{-7}$). The authors genotyped the polymorphic locus in two independent groups consisting of 1783 Scottish T2DM patients (the other part of the GoDARTS study) and 1113 patients involved in the UKPDS study (UK Prospective Diabetes Study) in order to replicate the original results of the genome-wide study. Significant association with response to MF therapy was found in both populations. The cumulative effect in attaining the objectives of hypoglycemic MF therapy was statistically significant at the genome-wide level (OR=1.35, 95% CI 1.22—1.49; p=2.9 × 10^{-7}). Later on, the same group of researchers have determined the genotypes of the polymorphic locus rs11212617 in three more cohorts: DCS, Rotterdam Study, and CARDS [8, 9]. Subsequent metaanalysis in five cohorts under study (the first one

was excluded in order to avoid biased results) included 4443 T2DM patients and it also confirmed the relationship between the minor C allele and attainment of target HbA1c level (OR= 1.25, 95% CI 1.13—1.38; p=7.8 × 10^{-6}). It is noteworthy that, when dividing the group into MF monotherapy and combination therapy subgroups, association of C allele was preserved only in the monotherapy subgroup. Van Leeuwen et al. hypothesized that some effects of MF therapy (particularly, AMPK-mediated ones, may partially be neutralized due to SU medications intake [10]. Possibly, this gene portion controls the cell cycle, and its changes can lead to decrease in phosphorylation and activation of AMPK, and therefore to different hypoglycemic effect of MF [10].
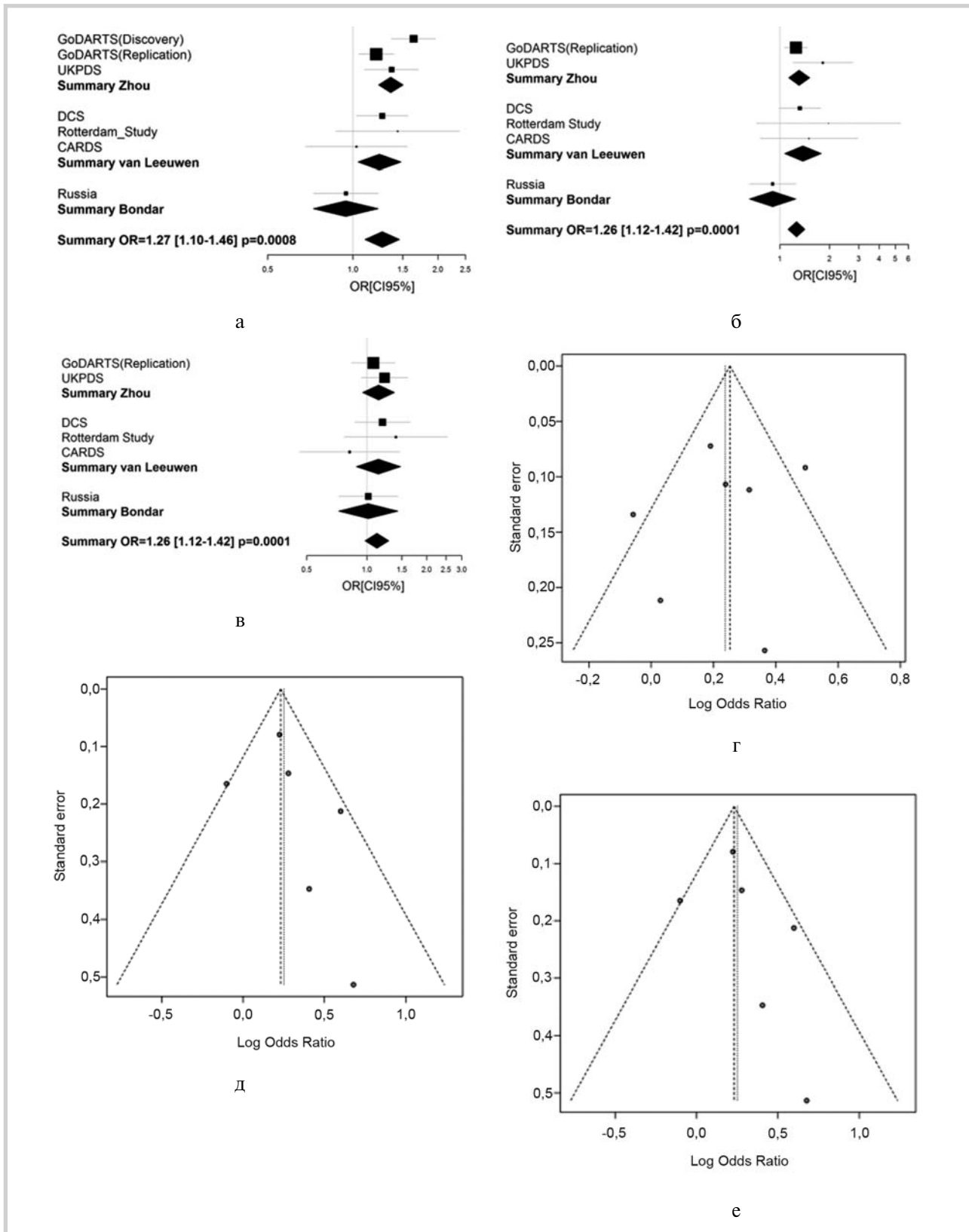
Figure 2. Graphical representation of the results of meta-analysis and bias analysis in publications.

A — «forest plot» for rs11212617 association with attainment of target HbA_{1c} level of <7% in the overall group; B — «forest plot» for rs11212617 association with attainment of target HbA_{1c} level of <7% in the group with metformin monotherapy, C — «forest plot» for rs11212617 association with attainment of target HbA_{1c} level of <7% in the group with combination therapy, D — «funnel plot» for rs11212617 association with attainment of target HbA_{1c} level of <7% in the overall group; E — «funnel plot» for rs11212617 association with attainment of target HbA_{1c} level of <7% in the group with metformin monotherapy, F — «funnel plot» for rs11212617 association with attainment of target HbA_{1c} level of <7% in the group with combination therapy.

Other researchers, who studied the effect of the polymorphic locus rs11212617 in the *ATM* gene on the likelihood of developing T2DM in patients with obesity and impaired glucose tolerance (IGT) involved in the Diabetes Prevention Program, DPP, including representatives of five American ethnic groups (n=988), suggested that the time of IGT conversion to T2DM in patients, who receive MF and have different genotypes of the polymorphic locus rs11212617, may differ. However, no significant difference was found. Florez et al. suggested that the effect of the polymorphic locus during MF treatment is noticeable only in the case of high HbA$_{1c}$, which is possible only in patients who were already diagnosed with T2DM. In the patients involved in their study, T2DM developed later and HbA$_{1c}$ levels were low [11].

Recently, Vilvanathan et al. evaluated association of polymorphic locus rs11212617 with the development of T2DM in the residents of South India (118 T2DM patients and 112 healthy controls). However, this polymorphic locus had no effect on predisposition to T2DM: OR=1.09, 95% CI 0.75—1.60 [12].

CONCLUSION

Our study showed no association of polymorphic locus rs11212617 in the *ATM* gene with response to MF therapy in T2DM patients in the Novosibirsk region. However, meta-analysis of our own data with previously published reports confirms the association of C allele with attainment of target HbA1c level (overall OR=1.27, 95% CI 1.10—1.46; p=0.0008). Thus, polymorphic locus rs11212617 in the *ATM* gene may influence the effectiveness of MF therapy in T2DM patients.

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