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Association study between *BGLAP* RS1800247-polymorphic variant and type 2 diabetes mellitus development among hypertensive and non-hypertensive Ukrainians

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Key words: type 2 diabetes mellitus, hypertension, osteocalcin, single nucleotide polymorphism, TT-homozygote, TC-heterozygote, CC-homozygote.

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The risk of type 2 diabetes mellitus (T2DM) development depends on a hereditary predisposition. According to the current data, bone tissue enhances insulin gene expression in pancreatic β-cells as well as increases insulin sensitivity of adipocytes, myocytes and hepatocytes through the secretion of undercarboxylated osteocalcin (unOCN).

The aim. To analyze the relation between rs1800247 SNP and T2DM occurrence depending on the arterial hypertension (AH) presence, as well as association between rs1800247 and systolic, diastolic, pulse, mean blood pressure among patients with T2DM.

Materials and methods. This study included 153 patients with diagnosed T2DM and 311 individuals without any carbohydrate metabolism disorders. Polymerase chain reaction-restriction fragment length polymorphism analysis (PCR-RFLP) was used for *BGLAP* rs1800247-genotyping. Logistic regression with interaction term "genotype × AH" was used to estimate the association between *BGLAP* rs1800247-genotypes and T2DM development in dominant, recessive, over-dominant and additive models of inheritance. Linear regression was performed to examine the influence of minor C-allele on the arterial blood pressure. Lipid profile characteristics of T2DM patients were stratified by rs1800247-genotype using ANOVA with Bonferroni post hoc test. All calculations were performed using Statistical Package for the Social Sciences software (SPSS, version 22.0, Chicago, IL, USA). A value of $P < 0.05$ was considered as significant.

Results. No association was found between rs1800247 single nucleotide polymorphism and T2DM development neither in AH patients, nor in subjects without AH ($P_a^{int\,b} > 0.05$). There was no impact of rs1800247 genotypes on systolic, diastolic, pulse and mean blood pressure among patients with T2DM ($P > 0.05$). It was showed that T2DM non-hypertensive CC-carriers had significantly lower levels of total cholesterol ($P = 0.012$) and LDL cholesterol ($P = 0.04$), but higher concentration of HDL cholesterol ($P = 0.015$) compared to the TT-genotype.

Conclusions. It was showed that CC-carriers had more favorable parameters of lipid metabolism among T2DM non-hypertensive Ukrainians. However, there was no association between rs1800247 SNP and T2DM development as well as blood pressure parameters.

Ключові слова: цукровий діабет 2 типу, артеріальна гіпертензія, остеокальцин, однонуклеотидний поліморфізм, ТТ-домінантна гомозигота, ТС-гетерозигота, СС-рецесивна гомозигота.

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Вивчення зв'язку між RS1800247-поліморфним варіантом гена *BGLAP* і розвитком цукрового діабету 2 типу серед українців з артеріальною гіпертензією та нормальним артеріальним тиском

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Ризик виникнення цукрового діабету 2 типу (ЦД2) залежить від генетичної схильності. За сучасними даними, кісткова тканина підвищує експресію гена інсуліну β-клітинами підшлункової залози, а також збільшує чутливість адипоцитів, міоцитів і гепатоцитів до інсуліну шляхом продукування декарбоксильованого остеокальцину (unOCN).

Мета роботи – проаналізувати зв'язок між rs1800247-однонуклеотидним поліморфізмом і виникненням ЦД2 залежно від наявності артеріальної гіпертензії (АГ), а також зв'язок між rs1800247 і систолічним, діастолічним, пульсовим, середнім кров'яним тиском в осіб із ЦД2.

Матеріали та методи. У дослідження залучили 153 пацієнтів з діагностованим ЦД2 і 311 осіб без будь-яких порушень вуглеводного обміну. Генотипування осіб за rs1800247-поліморфізмом гена *BGLAP* виконали за допомогою полімеразної ланцюгової реакції з аналізом довжини рестрикційних фрагментів (PCR-RFLP). Для оцінювання зв'язку між генотипами за rs1800247-поліморфізмом гена *BGLAP* і розвитком ЦД2 застосували логістичну регресію (враховуючи незалежну змінну «генотип × АГ») у межах домінантної, рецесивної, наддомінантної та адитивної моделей спадкування.

Для дослідження впливу мінорного С-алеля на рівень артеріального тиску використали метод лінійної регресії. Показники ліпідного обміну в пацієнтів із ЦД2 залежно від rs1800247-генотипу порівнювали за допомогою однофакторного дисперсійного аналізу та тесту Бонферроні. Усі розрахунки виконали, використовуючи програму для статистичного опрацювання даних SPSS 22.0. Значення $p < 0,05$ свідчило про статистичну значущість результатів.

Результати. Встановили відсутність зв'язку між rs1800247-однонуклеотидним поліморфізмом і розвитком ЦД2 і в осіб з АГ, і в обстежених із нормальним артеріальним тиском ($p_a^{int\,b} > 0,05$). Вплив генотипів за rs1800247-поліморфізмом на рівні систолічного, діастолічного, пульсового та середнього тиску в осіб із ЦД2 відсутній ($p > 0,05$). Однак носії СС-генотипу у

групі хворих на ЦД2 без АГ мають істотно нижчий рівень загального холестеролу (p = 0,012), ЛПНЩ (p = 0,04) і вищий рівень ЛПВЩ (p = 0,015) порівняно з ТТ-генотипом.

Висновки. Виявили, що носії СС-генотипу мають сприятливіші показники ліпідного метаболізму серед українців із ЦД2 та без АГ. Але відсутній зв'язок між rs1800247-однонуклеотидним поліморфізмом, виникненням ЦД2 і показниками артеріального тиску.

Изучение связи между RS1800247-полиморфным вариантом гена *BGLAP* и развитием сахарного диабета 2 типа среди украинцев с артериальной гипертензией и нормальным артериальным давлением

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Ключевые слова: сахарный диабет 2 типа, артериальная гипертензия, остеокальцин, однонуклеотидный полиморфизм, ТТ-доминантная гомозигота, ТС-гетерозигота, СС-рецессивная гомозигота.

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Риск возникновения сахарного диабета 2 типа (СД2) зависит от генетической предрасположенности. В соответствии с современными данными, костная ткань увеличивает экспрессию гена инсулина β-клетками поджелудочной железы, а также повышает чувствительность адипоцитов, миоцитов и гепатоцитов к инсулину путём продукции декарбоксилированного остеокальцина (unOCN).

Цель работы – проанализировать связь между rs1800247-однонуклеотидным полиморфизмом и возникновением СД2 в зависимости от наличия артериальной гипертензии (АГ), а также связь между rs1800247 и систолическим, диастолическим, пульсовым, средним кровяным давлением у пациентов с СД2.

Материалы и методы. В исследование включили 153 пациента с диагностированным СД2 и 311 лиц без каких-либо нарушений углеводного обмена. Генотипирование участников исследования по rs1800247-полиморфизмом гена *BGLA*P проведено при помощи полимеразной цепной реакции с анализом длины рестрикционных фрагментов (PCR-RFLP). Для оценки связи между rs1800247-полиморфизмом гена *BGLAP* и развитием СД2 использована логистическая регрессия (с учётом независимой переменной «генотип × АГ») в пределах доминантной, рецессивной, сверхдоминантной и аддитивной моделей наследования.

Для исследования влияния минорного С-аллеля на уровень артериального давления использован метод линейной регрессии. Показатели липидного обмена у пациентов с СД2 в зависимости от rs1800247-генотипа сравнивали при помощи однофакторного дисперсионного анализа и теста Бонферрони. Все расчёты проведены с использованием программы для статистической обработки данных SPSS 22.0. Значение p < 0,05 свидетельствовало о статистической значимости результатов.

Результаты. Установлено отсутствие связи между rs1800247-однонуклеотидным полиморфизмом и развитием СД2 среди лиц и с АГ, и с нормальным артериальным давлением ($p_a^{int\,b}$ > 0,05). Влияние генотипов по rs1800247-полиморфизму на уровни систолического, диастолического, пульсового и среднего давления у лиц с СД2 отсутствует (p > 0,05). Однако носители СС-генотипа в группе больных СД2 без АГ имеют значительно более низкий уровень общего холестерола (p = 0,012), ЛПНП (p = 0,04) и более высокий уровень ЛПВП (p = 0,015) в сравнении с ТТ-генотипом.

Выводы. Установлено, что носители СС-генотипа имеют более благоприятные показатели липидного метаболизма среди украинцев с СД2 и без АГ. Однако отсутствует связь между rs1800247-однонуклеотидным полиморфизмом и возникновением СД2, а также показателями артериального давления.

Nowadays it is known about at least two proteins of bone tissue that could influence on systemic energy metabolism. The first one is undercarboxylated osteocalcin (unOCN), which directly stimulates insulin production in pancreatic β-cells and increases peripheral tissue sensitivity to this hormone. The second one, osteotesticular tyrosine phosphatase (OST-PTP), regulates OCN gene expression in accordance with metabolic requirements of the bone tissue [1]. Bone reparation was the priority process of energy substrate distribution in animals, as the integrity of bones was vitally needed. Thus, active OST-PTP dephosphorylates the β-subunits of insulin receptor that leads to inhibition of metabolic and proliferative effects of this hormone. The consequence is the decreased rate of Runx 2, which is the crucial transcription factor for OCN gene expression. Temporary reducing of unOCN level in systemic circulation leads to hypoinsulinaemia, as well as decreased adipose, muscle and liver tissue sensitivity to insulin. As the result, more glucose reaches a bone cell that is important for synthesis and resorption of bone tissue [1–3].

The involvement of unOCN in the energy metabolism was confirmed in experimental and clinical studies. It is known that OCN gene-knockout mouse (*Bglap*$^{-/-}$) have increased bone tissue formation without the influence on bone resorption. In the same time their phenotype was opposite to OST-PTP gene-knockout mouse (*Ptprv*$^{-/-}$), which showed an impaired glucose tolerance and overweight [4,5]. unOCN binds to specific GPRC6A receptors and enhances insulin and adiponectin expression, as well as β-cell proliferation [6].

Meta-analysis indicates the presence of reverse correlation between OCN plasma concentration and insulin, fasting glucose and glycated hemoglobin in patients with type 2 diabetes mellitus (T2DM) [7]. Moreover, rs1800247-single nucleotide polymorphism (SNP) of *BGLAP* gene was associated with decreased risk of arterial hypertension (AH) and lower diastolic blood pressure [8].

Aim

Therefore, the aim of this study was to analyze the relation between rs1800247 SNP and T2DM occurrence depending on the AH presence, as well as association between rs1800247 and systolic, diastolic, pulse, mean blood pressure among patients with T2DM.

Table 1. Characteristics of the study population

With AH			
Parameters, units	**T2DM (n = 107)**	**Control (n = 156)**	**P**
Age, years	64.49 ± 8.11	69.53 ± 11.31	< 0.001
Sex, female/male	56/52	101/55	0.036
Body mass index, kg/m^2	29.7 ± 4.98	27.62 ± 4.69	0.001
Current smokers, n (%)	36 (33.3)	48 (30.8)	0.66
Fasting glucose, mmol/L	10.35 ± 3.77	5.22 ± 0.68	<0.001
Total cholesterol, mmol/L	5.24 ± 1.18	4.56 ±1.26	<0.001
HDL cholesterol, mmol/L	0.94 ± 0.28	1.09 ± 0.28	<0.001
LDL cholesterol, mmol/L	3.36 ± 1.16	2.8 ± 1.22	0.003
Triglyceride, mmol/L	1.76 ± 0.66	1.44 ± 0.65	0.002
Systolic BP, mmHg	151.71 ± 14.78	174.46 ± 22.69	<0.001
Diastolic BP, mmHg	92.31 ± 8.6	97.05 ± 13.89	0.002
Pulse BP, mmHg	59.4 ± 13.43	77.4 ± 19.32	<0.001
Mean BP, mmHg	112.12 ± 9.06	122.85 ± 14.74	<0.001
Without AH			
Parameter, units	**T2DM (n = 46)**	**Control (n = 155)**	**P**
Age, years	65.26 ± 8.49	61.75 ± 12.61	0.078
Sex, female/male	23/23	51/104	0.035
Body mass index, kg/m^2	28.35 ± 4.74	27.38 ± 4.72	0.222
Current smokers, n (%)	14 (30.4)	43 (27.7)	0.722
Fasting glucose, mmol/L	9.86 ± 2.57	5.23 ± 0.73	<0.001
Total cholesterol, mmol/L	5.65 ± 1.35	4.14 ± 1.15	<0.001
HDL cholesterol, mmol/L	0.96 ± 0.31	1.09 ± 0.19	0.038
LDL cholesterol, mmol/L	3.54 ± 1.39	2.48 ± 1.12	0.001
Triglyceride, mmol/L	2.22 ± 2.49	1.25 ± 0.51	0.051
Systolic BP, mmHg	126.09 ± 8.02	126.84 ± 11.09	0.67
Diastolic BP, mmHg	79.67 ± 4.76	79.58 ± 7.05	0.933
Pulse BP, mmHg	46.41 ± 6.02	47.26 ± 9.01	0.551
Mean BPs, mmHg	95.14 ± 5.34	95.33 ± 7.49	0.874

AH: arterial hypertension; **T2DM:** type 2 diabetes mellitus; **HDL:** high density lipoproteins; **LDL:** low density lipoproteins; BP: blood pressure.

Materials and methods

Study population and genotyping. This study included 153 patients (75 females and 78 males; mean age [±SD] 64.67 ± 8.2 year) with diagnosed T2DM and 311 individuals (106 females and 205 males; mean age 65.65 ± 12.58 year) without any carbohydrate metabolism disorders. Final T2DM diagnosis was determined in the presence of specific clinical manifestations (polydipsia, polyuria, polyphagia and weight loss), fasting glucose level and glucose tolerance test results according to the World Health Organization criteria (WHO, 1999).

Relatively healthy subjects without any carbohydrate metabolism disorders (which was confirmed by a fasting plasma glucose level less than 5.6 mmol/L and a 75 g oral glucose tolerance test result less than 7.8 mmol/L) and negative family history of diabetes were enrolled in the control group. All the examined individuals were selected from hospital records in the 5th Sumy Clinical Hospital and Sumy Regional Diagnostic Center between 2011–2019. AH was diagnosed in 107 T2DM patients and 156 control subjects with systolic blood pressure higher than 140 mmHg and/or diastolic blood pressure higher than 90 mmHg and no antihypertensive therapy (according to the WHO, 1999). Polymerase chain reaction-restriction fragment length polymorphism analysis (PCR-RFLP) was used for *BGLAP* rs1800247-genotyping. Full information about genotyping protocol was presented in our previous research [9].

The study design complies with the Declaration of Helsinki and was approved by the Ethic Committee of Medical Institute of Sumy State University and the Ethic Committee of Medical Institute of Sumy State University (number 4/02.18.09). A written informed consent was obtained from all participants.

Statistical analysis. Continuous variables were presented as the mean ± SD, categorical – as absolute and percentage values. Chi square (χ^2) test was used for comparing the categorical variables. Two-tailed Student's t-test was used to compare the mean values of two groups (with preliminary verification of the data distribution for normality through the Shapiro-Wilk test). The mean values of three groups were compared using ANOVA with further Bonferroni post hoc test. Logistic regression with interaction term "genotype × AH" was used for the association analysis between four models of inheritance: dominant, recessive, over-dominant and additive.

The adjustment for age, sex, smoking and body mass index (BMI) was used to exclude the influence of other T2DM risk factors. Bonferroni correction was applied for accurate results. The impact of rs1800247-C minor allele on systolic, diastolic, pulse and mean arterial blood pressure among diabetic patients was estimated via linear regression. All calculations were performed using Statistical Package for the Social Sciences software (SPSS, version 22.0, Chicago, IL, USA). A value of $P < 0.05$ was considered as significant.

Results

The clinical characteristics of compared groups are shown in *Table 1*. Statistically significant differences in age, sex, BMI, fasting glucose, lipid profile and blood pressure parameters ($P < 0.05$), but not among smokers ($P = 0.66$), was found in groups with AH. In contrast, T2DM patients and controls without AH were comparable in age, BMI, smoking status, triglyceride concentration and blood pressure parameters ($P > 0.05$), but not in sex, fasting glucose levels, total cholesterol, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol concentrations ($P < 0.05$).

Logistic regression with interaction term was used to study the influence of rs1800247 genotypes on the T2DM development There was no statistically significant associations neither in AH patients, nor in non-AH individuals in all models of inheritance (*Table 2*).

Then we performed the linear regression models to compare the rs1800247 genotype impact on the arterial blood pressure values. No significant differences were found for systolic, diastolic, pulse and mean arterial blood pressure among T2DM patients (*Table 3*).

Table 4 indicates the parameters of lipid profile in T2DM patients with and without AH stratified by rs1800247 genotypes. Statistically significant differences were found between TT and CC carriers in total cholesterol ($P = 0.012$), HDL cholesterol ($P = 0.015$) and LDL cholesterol ($P = 0.04$) concentrations among T2DM individuals without AH.

Table 2. Association analysis between *BGLAP* rs1800247 and T2DM development among AH and non-AH individuals

Regression model[1]	Covariate	P_c	OR_c (95 % CI)	P_c^{int}	P_a	OR_a (95 % CI)	P_a^{int}	P_a^{b}	$P_a^{int\,b}$
Dominant	TC+CC vs TT	0.268	0.748 (0.448–1.25)	0.976	0.199	0.708 (0.417–1.200)	0.754	0.796	1
		0.429	0.758 (0.382–1.506)		0.565	0.814 (0.405–1.639)		1	
Recessive	CC vs TT+TC	0.681	1.264 (0.413–3.873)	0.412	0.674	1.279 (0.406–4.036)	0.367	1	1
		0.11	2.433 (0.818–7.242)		0.082	2.662 (0.883–8.027)		0.382	
Over-dominant	CT vs TT+CC	0.183	0.696 (0.408–1.187)	0.504	0.131	0.655 (0.378–1.134)	0.653	0.524	1
		0.084	0.505 (0.233–1.095)		0.109	0.525 (0.239–1.156)		0.436	
Additive	CT vs TT	0.199	0.702 (0.409–1.205)	0.622	0.149	0.664 (0.381–1.157)	0.779	0.596	1
		0.14	0.552 (0.25–1.215)		0.181	0.577 (0.258–1.291)		0.724	
	CC vs TT	0.841	1.123 (0.361–3.387)	0.468	0.833	1.135 (0.351–3.673)	0.363	1	1
		0.215	2.022 (0.665–6.151)		0.127	2.422 (0.778–7.539)		0.508	

1: Upper row shows the results for individuals with AH and lower row – for those without AH; **Pc:** crude value; **Pcint:** crude value for interactive term; **Pa:** value adjusted for age, sex, smoking status, and body mass index; **Paint:** value adjusted for age, sex, smoking status, and body mass index for interaction term; **Pab:** value adjusted for Bonferroni correction; **Paint b:** value adjusted for Bonferroni correction for interaction term; **T2DM:** type 2 diabetes mellitus; **AH:** arterial hypertension, **TT:** homozygous dominant, **TC:** heterozygous, **CC:** homozygous recessive.

Discussion

It is known that T2DM patients have lower carboxylated osteocalcin (cOCN) and unOCN concentrations than relatively healthy subjects [10,11]. The meta-analysis showed significantly decreased baseline serum total OCN in T2DM compared with non-T2DM subjects. Moreover, a unit elevation in serum total OCN was correlated with a mean increase in HOMA-B, as well as mean reduction in HbA1c, fasting plasma glucose, HOMA-IR and BMI [12].

In this study, we continued to study the association between *BGLAP* rs1800247 SNP and T2DM development among Ukrainians. The lack of studied correlation matches both our previous research [9] and Das et al. study, which excluded *BGLAP* rs1800247 SNP as a T2DM potential risk factor [13].

Cardiovascular diseases are widespread chronic complications in patients with T2DM. Animal and in vitro studies showed the protective effect of unOCN on vessels. This was explained by the enhanced expression of endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) production [14]. Lower serum OCN concentration was found among hypertensive men, but not women. Moreover, serum OCN level was inversely associated with systolic blood pressure in Chinese men, but not women [15].

Another study showed that *BGLAP* rs1800247 was associated with lower risk of AH and diastolic blood pressure in Chinese population [8]. In contrast, our study indicates no relation between *BGLAP* rs1800247 and blood pressure level among T2DM Ukrainians that can be explained by ethnic differences. Despite this, in present study, we showed that T2DM non-hypertensive CC-carriers had significantly lower levels of total cholesterol and LDL cholesterol, but higher concentration of HDL cholesterol compared to those in the TT-genotype. The results obtained may indicate more favorable conditions for the lipid metabolism in CC-homozyguous of the examined groups among Ukrainians.

Conclusions

1. Non-hypertensive T2DM CC-carriers had significantly lower levels of total cholesterol (P = 0.012) and LDL cholesterol (P = 0.04), but higher concentration of HDL cholesterol (P = 0.015) compared to the TT-genotype in Ukrainian population.

Table 3. Association analysis between *BGLAP* rs1800247 and blood pressure value among T2DM patients

Regression model	B	P	r^2
Systolic blood pressure			
TC vs TT	2.363	0.476	0.01
CC vs TT	-4.596	0.396	
Constant	143.762	<0.001	
Diastolic blood pressure			
TC vs TT	-0.239	0.895	<0.001
CC vs TT	-0.281	0.925	
Constant	88.614	<0.001	
Pulse blood pressure			
TC vs TT	2.601	0.291	0.018
CC vs TT	-4.315	0.284	
Constant	55.149	<0.001	
Mean blood pressure			
TC vs TT	0.625	0.768	0.003
CC vs TT	-1.722	0.62	
Constant	107	<0.001	

B: regression coefficient; **r2:** r-squared value; **T2DM:** type 2 diabetes mellitus; **TT:** homozygous dominant; **TC:** heterozygous; **CC:** homozygous recessive.

Table 4. Lipid profile in T2DM patients with and without AH stratified by *BGLAP* rs1800247 genotypes

With AH					
Parameters, units	**Genotype**			**F**	**P**
	TT (n = 71)	**TC (n = 30)**	**CC (n = 6)**		
Total cholesterol, mmol/L	5.26 ± 1.22	5.19 ± 1.11	5.14 ± 1.28	0.057	0.945
HDL cholesterol, mmol/L	0.96 ± 0.28	0.86 ± 0.27	1.05 ± 0.22	2.004	0.14
LDL cholesterol, mmol/L	3.33 ± 1.17	3.42 ± 1.14	3.36 ± 1.22	0.065	0.937
Triglyceride, mmol/L	1.73 ± 0.66	1.88 ± 0.65	1.58 ± 0.75	0.763	0.469
Without AH					
Parameters, units	**Genotype**			**F**	**P**
	TT (n = 30)	**TC (n = 10)**	**CC (n = 6)**		
Total cholesterol, mmol/L	5.95 ± 1.32	5.04 ± 1.23	4.27 ± 0.54	5.666	0.007[1]
HDL cholesterol, mmol/L	0.94 ± 0.26	1.01 ± 0.39	1.32 ± 0.12	4.368	0.019[2]
LDL cholesterol, mmol/L	3.8 ± 1.41	2.85 ± 1.07	2.33 ± 0.63	4.53	0.016[3]
Triglyceride, mmol/L	2.43 ± 3.04	1.88 ± 0.74	1.68 ± 0.62	0.332	0.719

AH: arterial hypertension; **T2DM:** type 2 diabetes mellitus; **HDL:** high density lipoproteins; **LDL:** low density lipoproteins; **1:** significant difference between the TT and CC genotypes (P = 0.012) by Bonferroni post hoc test; **2:** significant difference between the TT and CC genotypes (P = 0.015) by Bonferroni post hoc test; **3:** significant difference between the TT and CC genotypes (P = 0.04) by Bonferroni post hoc test; **TT:** homozygous dominant, **TC:** heterozygous, **CC:** homozygous recessive.

2. No association was found between rs1800247 SNP and T2DM development among hypertensive Ukrainians ($P_a^{int\,b} > 0.05$).

3. No association was found between rs1800247 SNP and T2DM development among non-hypertensive Ukrainians ($P_a^{int\,b} > 0.05$).

4. There was no relation between rs1800247 SNP and blood pressure parameters (systolic, diastolic, pulse and mean blood pressure) among T2DM Ukrainians ($P > 0.05$).

Perspectives for further research. Further studies with extended groups of comparison are needed for the confirmation of results. Moreover, it will be useful to study the association between other *BGLAP* SNPs and T2DM and AH development.

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