UDC 575.113:[616.12-008.331.1+616.857]

DOI: 10.20333/25000136-2023-5-88-94

The RS7314935 (117718837 g>a) is biomarker of arterial hypertension and tension-type headache phenotype

M. M. Petrova [1], P. A. Reznichenko [1], P. V. Alyabyeva [1], I. V. Romanova [1], R. F. Nasyrova [2] , N. A. Shnayder [1,2]

[1] Shared Core Facilities Molecular and Cell Technologies, Prof. V.F. Voino-Yasenetsky Krasnoyarsk State Medical University, 660022 Krasnoyarsk, Russian Federation

[2] Institute of Personalized Psychiatry and Neurology, V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology, 192019 Saint Petersburg, Russian Federation

The aim of the research. The purpose of the study was to investigate the association of alleles (G>A) and genotypes (GG, GA, AA) carriage of SNP rs7314935 of the NOS1 gene with the «AH+TTH» phenotype development in middle-aged adults.

Material and methods. There was open, observational, cross-sectional, case-control study. Study period is October 2020 – July 2022. Study location is Professor V.F. Voino-Yasenetsky Krasnoyarsk State Medical University (KrasSMU). We included in the study: residents of the Krasnoyarsk (industrial city of the Siberia); Caucasians; persons of average (from 45 to 65 years) age; compliance with the protocol of the research; have a signed informed consent form to participate in the study. We exclude from the study: residents of other regions and members of small ethnic Siberian groups; Asians; age up to 45 years and over 65 years; comorbid somatic diseases (cognitive disorders; acute infectious process; diabetes and chronic kidney disease; chronic heart failure; other primary headaches (except TTH); secondary headaches); low compliance; refusal to sign the informed consent form for participation in the study. The sample was 91 complex observed participants: group 1 (hypertensive patients) – 60 patients; group 2 (control) – 31 healthy volunteers. Group 1 was divided into two subgroups: main subgroup – «AH+TTH» (30 patients) and comparable subgroup – AH without headache (30 patients). Venous blood was taken on an empty stomach for each participant. Genomic deoxyribonucleic acid (DNA) was isolated from leukocyte suspension according to the standard protocol [23]. The determination of the carriage of polymorphic allelic variants of rs7314935 of the NOS1 gene was carried out using real-time polymerase chain reaction (RT-PCR), on the apparatus Rotor-Gene 6000 (Australia) using TaqMan allelic discrimination technology and commercially available fluorescent probes (primers) developed by Applied Biosystems (USA).

Results. There were not statistically significantly differences (p>0,05) between groups 1 and 2 in average age and gender distribution. The main (AH+TTH) and comparable (AH without headache) subgroups were comparable (p>0,05) by course and lasting of AH anamnesis, and average age of AH onset. The onset age of AH was slightly higher than the onset age of TTH. There were 4 main triggers for elevation of BP in patients with AH (group 1). Three triggers did not significantly differ (p>0,05) in main subgroup (AH+TTH) and comparable (AH without headache) subgroups: emotional and physical overload, and also sleep problems (sleep deprivation, lack of sleep, oversleeping). But headache episodes themselves were statistically significant trigger for elevation of BP in patients of main subgroup (AH+TTH) compared subgroup of hypertensive patients without headache (p=0,002).

Conclusion. Our study was shown that the heterozygous genotype GA of rs7314935 of the NOS1 gene may be new genetic biomarker of «AH+TTH» phenotype developing in Caucasian hypertensive patients from East Siberia.

Key words: arterial hypertension; tension-type headache; genetic biomarker; nNOS; NOS1 gene; rs7314935.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest associated with the publication of this article.

Citation: Petrova MM, Reznichenko PA, Alyabyeva PV, Romanova IV, Nasyrova RF, Shnayder NA. The RS7314935 (117718837 g>a) is biomarker of arterial hypertension and tension-type headache phenotype. *Siberian Medical Review.* 2023;(5):88-94. DOI: 10.20333/25000136-2023-5-88-94

Introduction

Arterial hypertension (AH) is a syndrome of clinically increased blood pressure (BP) in patients with essential AH and symptomatic AH above the normal value (systolic BP – more than 140 mmHg and diastolic BP – more than 90 mmHg). These values were associated with high cardiovascular risk in epidemiological randomised controlled studies which, in result, have demonstrated the feasibility and benefit of hypotensive treatment [1].

Tension-type headache (TTH) is one of the most common forms of primary headache, manifested by bilateral pressing or constricting headache of mild or moderate intensity lasting from 30 minutes to several days. Headache in TTH patients does not increase with normal physical activity and is not accompanied by nausea, but there may be an appetite decrease, photo- or phonophobia [2].

The prevalence of AH covers from 30% to 45% of the adult Russian population. Hypertension patients older than 60 years are more 60% of the population [3]. According to epidemiological studies, the prevalence of TTH also varies from 30% to 75% in the world and in Russia [4]. Every year, there is a tendency for the rising prevalence of these diseases, probably due the sociological and climatic problems of the society.

AH and TTH are often comorbid conditions. The clinical phenotype or overlap syndrome «AH+TTH» is a common problem for physicians, cardiologists and neurologists. The nature of pathophysiological and clinical relationship between AH and TTH is a very relevant problem, although poorly understood [5].

Among the variety of biologically active substances produced by the endothelium, the most important one is nitric oxide (NO). It is known that NO plays a role in adaptation of the vascular system to various metabolic changes. Normally, this molecule is constantly released to keep blood vessels in dilation. NO is formed due to the action of NO-synthase (NOS) through oxidation of the guanidine nitrogen atom in L-arginine under the influence of catabolic reactions of the calmodulin-dependent isoform of the NOS enzyme [6]. Due to various pathological changes in blood vessels, the ability of endothelial cells to release this relaxing factor decreases, which leads to endothelial dysfunction [7]. Endothelial dysfunction is in turn one of the main links in AH pathogenesis [8].

The modern theory of TTH pathogenesis is that neurobiological and vascular component is one of the main its mechanisms. There is a disturbance between the arterial and venous circulatory system. When the venous outflow is impaired, the venous sinuses overflow, which leads to irritation of the trigeminal nerve [9]. NO is also responsible for neuro- and neuromuscular transmission. Thus, muscle spasm (in TTH with tension of pericranial muscles) leads to venous stagnation and endothelial dysfunction [10].

Therefore, the pathogenetic mechanism common to AH and TTH is endothelial dysfunction due to the disturbance of NO synthesis, which explains the new hypothesis of the «AH+TTH» phenotype development [11].

There are three isoforms of NOS: neuronal (nNOS), inducible (iNOS) and endothelial (eNOS) [11]. Functional activity of these isoforms of NOS depends on the major (wild type) and minor alleles of single nucleotide polymorphisms (SNPs) of *NOS1, NOS2*, and *NOS3* genes [12]. As is known, eNOS is mainly expressed in cells of vascular walls. It is the main regulator of BP through its influence on vasodilation. And nNOS, in turn, is mainly expressed in the brain. However, nNOS is also expressed in cells of the skeletal muscle [13] and in endothelial cells, cardiomyocytes, thus nNOS is

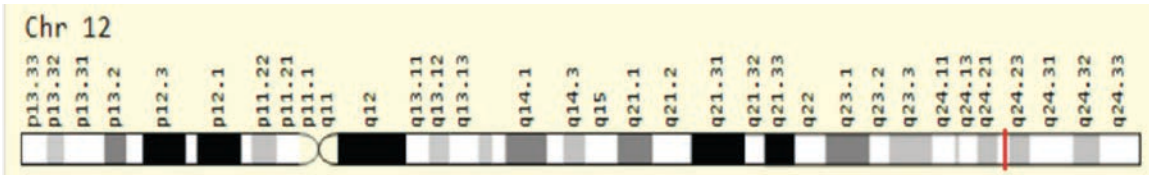


Figure 1. NOS1 gene chromosome localization (in human) [15].

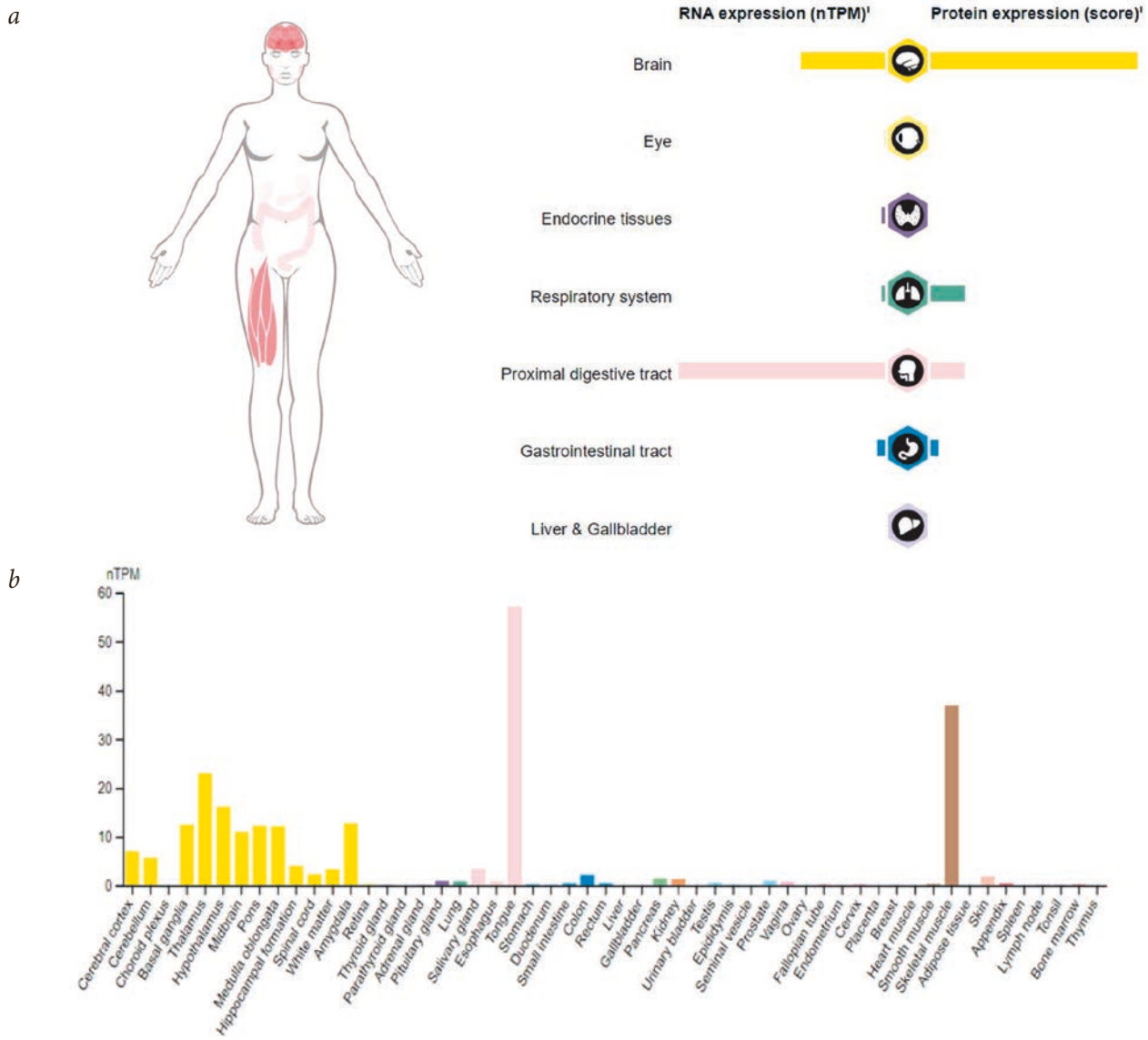


Figure 2. Expression levels of nNOS in the human body (a) and tissues (b) [18].

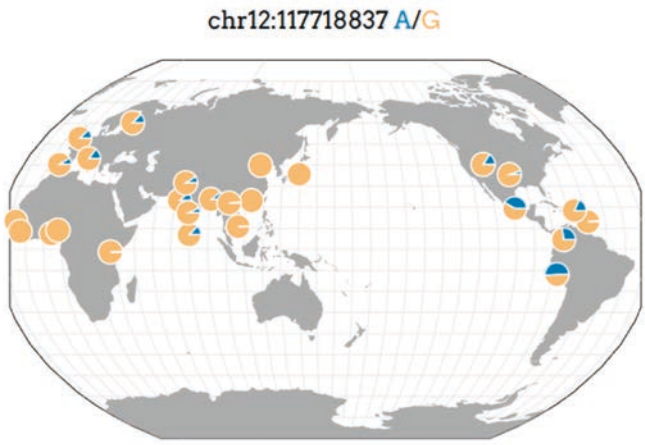


Figure 3. Geography of genetic variant rs7314935 of the NOS1 gene in the world [19].

also important in vascular tone regulation (control of vasodilation) [14]. Therefore, nNOS may be an important biomarker for the «AH+TTH» phenotype development.

The *NOS1* gene encoding nNOS is localised on the long arm of chromosome 12 – on 12q24 (see Figure 1) [15, 16]. Low-functional SNP rs7314935 (position: 12:117718837 (GRCh37), NC_000012.12:117281031:G:A) of the *NOS1* gene, leading to replacement of guanine with adenine – intron variant – can lead to a decrease in the functional activity of nNOS, the absence of the expected physiological synthesis of NO in the brain, blood vessels and skeletal muscles (see Figure 2) [17, 18]. The carriage of major and minor alleles of this SNP in the Caucasian population from Siberia (Russia) is shown in Figure 3 [19].

The purpose of the study was to investigate the association of alleles (G>A) and genotypes (GG, GA, AA) carriage of SNP rs7314935 of the *NOS1* gene with the «AH+TTH» phenotype development in middle-aged adults.

The stages of the study were: 1) scientific search; 2) sampling; 3) molecular genetic testing; 4) statistical processing.

At first, we studied the aetiology, pathogenesis and clinical picture of TTH. Then we identified the main triggers for elevation of BP, and for episode of TTH in patients with AH. The scientific literature analysis has shown the relationship between nitric oxide dysfunction and endothelial dysfunction. We have studied the functions of the *NOS1* gene, and identified SNPs of this gene potentially associated with the risk of developing the phenotype.

We observed and examined patients with AH. And then randomise them into subgroups of a clinical «AH+TTH» phenotype and AH without headache. A control group of healthy volunteers was recruited. After that, there was creation of a database for study participants and the results were processed.

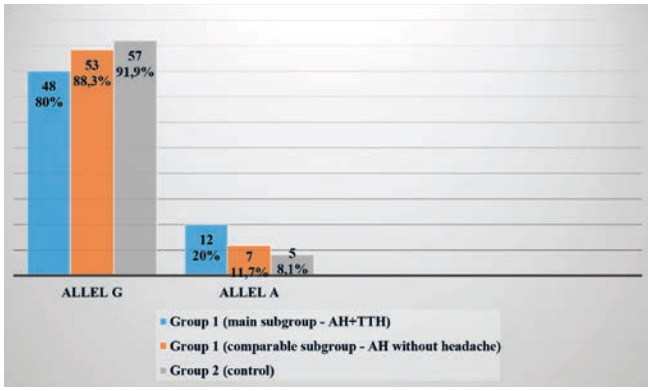
Finally, we analysed the carriage of major (G, guanine) and minor (A, adenine) alleles, as well as GG (guanine / guanine), GA (guanine / adenine), AA (adenine / adenine) genotypes in the main group, the comparison group and the control group; assessed the risks of developing AH and the «AH+TTH» phenotype as compared with the control group.

Material and methods

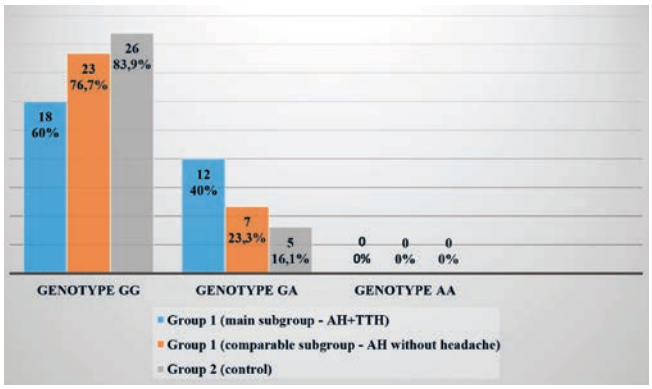
There was open, observational, cross-sectional, case-control study. Study period is October 2020 – July 2022. The research site was Professor V.F. Voino-Yasenetsky Krasnoyarsk State Medical University (KrasSMU). Table 1 presents the general information about the research.

The informed consent for the participation in this study was received from all patients and healthy volunteers. All participants were not rewarded for participating.

The study included: residents of Krasnoyarsk (an industrial city in Siberia); Caucasians; persons of middle (from 45 to 65 years) age; compliance with the protocol of the re-



a



b

Figure 4. The frequencies of rs7314935 alleles (a) and genotypes (b) in sample.

Table 1

Study characteristics

Document	Number	Date
Positive decision of the local ethics committee of the KrasSMU	101/2020	31.10.2020
Rector's order of the KrasSMU grant to support the young scientists research	462-base	12.01.2021
Registration card of research «Clinical and genetic predictors of the tension-type headache and arterial hypertension phenotype»	122030300108-6	03.03.2022

Note: KrasSMU – V.F. Voino-Yasenetsky Krasnoyarsk State Medical University.

search; have a signed informed consent form to participate in the study. The subjects excluded from the study were residents of other regions and members of small ethnic Siberian groups; Asians; age up to 45 years and over 65 years; comorbid somatic diseases (cognitive disorders; acute infectious process; diabetes and chronic kidney disease; chronic heart failure; other primary headaches (except TTH); secondary headaches); low compliance; refusal to sign the informed consent form for participation in the study.

The sample was 91 complex observed participants: group 1 (hypertension patients) – 60 patients; group 2 (control) – 31 healthy volunteers. Group 1 was divided into two subgroups: the main subgroup – «AH+TTH» (30 patients) and the comparison subgroup – AH without headache (30 patients). When diagnosing AH, the cardiologist used the criteria of the European Society of Cardiology and the European Society of Hypertension (2018) [20] and the criteria of the Russian Society of Cardiology (2020) [21]. When diagnosing TTH, the neurologist used the criteria of the International Classification of Headache Disorders (2018) [22].

Venous blood was sampled from fasted patients. Genomic deoxyribonucleic acid (DNA) was isolated from leukocyte suspension according to the standard protocol [23]. The determination of the carriage of polymorphic allelic variants of rs7314935 of the *NOS1* gene was carried out using real-time polymerase chain reaction (RT-PCR), on the Rotor-Gene 6000 apparatus (Australia) using TaqMan allelic discrimination technology and commercially available fluorescent probes (primers) developed by Applied Biosystems (USA).

Results were classed in data base in program Excel (version 14; USA) and analysed in statistical program SPSS (version 22; USA) and MedStatistic online calculator available at https://medstatistic.ru/. The distribution of genotypes of rs7314935 was checked for compliance with the Hardy-Weinberg equilibrium. Pairwise comparison of allele and genotype frequencies was performed using the chi-square test ($\chi 2$). If the expected frequencies were less than 5, then Fisher's exact test was used. Significance level was $p<0.05$. The risk of «AH+TTH» phenotype development, as well as AH, was assessed in odds ratio with 95% confidence interval (OR, 95% CI).

Results and discussion

Table 2 presents the general information about the study participants.

There were no statistically significantly differences ($p>0.05$) between groups 1 and 2 in average age and gender distribution. The main (AH+TTH) and comparison (AH without headache) subgroups were comparable ($p>0.05$) by course and lasting of AH anamnesis, and average age of AH onset. The onset age of AH was slightly higher than the onset age of TTH.

Classical risk factors for AH and TTH have been studied (smoker status, alcohol consumption, body mass index, level of physical activity). Statistically significant differences were obtained for the low physical activity ($p=0.034$) and obesity of the second ($p=0.039$) and third ($p=0.049$) degrees.

There were 4 main triggers for elevation of BP in patients with AH (group 1). Three triggers did not significantly differ ($p>0.05$) in the main subgroup (AH+TTH) and comparison (AH without headache) subgroups: emotional and physical overload, as well as sleep problems (sleep deprivation, lack of sleep, oversleeping). However, headache episodes on their own were a statistically significant trigger for elevation of BP in patients of the main subgroup (AH+TTH) compared to the subgroup of hypertensive patients without headache ($p=0.002$).

The carriage of rs7314935 alleles and genotypes in the studied sample was compliant with the Hardy-Weinberg Equilibrium law in all observation groups. The analysis is presented in table 3.

The frequencies of rs7314935 alleles and genotypes are presented in Figure 2.

There were no statistically significant differences (see Figure 2, Table 4) in alleles frequency ($p=0.142$) and genotype distribution ($p=0.111$) in comparing all patients with AH (n=60) regardless of the presence of comorbid headache: group 1 (main subgroup – AH+TTH) and group 1 (comparable subgroup – AH without headache) versus group 2 (control). Similar results were obtained in comparing group 1 (comparable subgroup – AH without headache) to group 2 (control): both in the analysis of allele frequencies ($p=0.504$) and genotype distribution ($p=0.479$).

Table 2

Participants' characteristics

General characteristics	Group 1 (main subgroup - AH+TTH)	Group 1 (comparable subgroup - AH without headache)	Group 2 (control)
Age of the study participants, years (Mean + standard deviation)	52.7 + 5.7	53.6 + 7.1	5.7 + 6.7
Female (%)	73.3	60.0	51.6
Male (%)	26.7	40.0	48.4
Duration of AH (anamnesis), years (Mean + standard deviation)	12.4 + 12.4	15.8 + 9.9	-
Age of AH onset, years (Mean + standard deviation)	40.6 + 11.7	37.8 + 11.5	-
Duration of TTH (anamnesis), years (Mean + standard deviation)	15.3 + 11.2	-	-
Age of TTH onset, years (Mean + standard deviation)	37.5 + 10.4	-	-

Note: AH – arterial hypertension; TTH – tension-type headache.

Table 3

The Hardy-Weinberg equilibrium

Group	Genotype	Participants	Hardy-Weinberg Equilibrium	X2	p
Group 1 (main subgroup – AH+TTH) n1=30	GG	18 (60%)	19.2	1.875	0.39
	GA	12 (40%)	9.6		
	AA	0 (0%)	1.2		
Group 1 (comparable subgroup – AH without headache) n2=30	GG	23 (76.7%)	23.41	0.523	0.77
	GA	7 (23.3%)	6.183		
	AA	0 (0%)	0.408		
Group 2 (control) n3=31	GG	26 (83.9%)	26.2	0.238	0.89
	GA	5 (16.1%)	4.596		
	AA	0	0.202		

Note: AH – arterial hypertension; TTH – tension-type headache. The genotype homozygous for the recessive allele (AA) was not found in the study sample.

Table 4

Odds Ratio of phenotype depending on allelic and genotype variants of rs7314935

Alleles, genotypes	χ2	p	Odds ratio	95% confidential interval
Group 1 (all hypertensive patients) / Group 2 (control)				
G	2.155	0.142	0.47	0.17–1.32
A			2.15	0.76–6.05
GG	2.541	0.111	0.42	0.14–1.25
GA			2.41	0.8–7.25
AA			-	-
Group 1 (main subgroup – AH+TTH) / Group 2 (control)				
G	3.622	0.057	0.35	0.12–1.067
A			2.85	0.94–8.66
GG	4.322	0.038*	0.61	0.09–0.96
GA			3.47	1.04–11.56
AA			-	-
Group 1 (comparable subgroup – AH without headache) / Group 2 (control)				
G	0.446	0.504	0.66	0.2–2.22
A			1.51	0.45–5.03
GG	0.501	0.479	0.63	0.18–2.27
GA			1.58	0.44–5.68
AA			-	-
Group 1 (main subgroup – AH+TTH) / Group 1 (comparable subgroup – AH without headache)				
G	1.563	0.211	0.53	0.19–1.45
A			1.89	0.69–5.2
GG	1.926	0.165	0.46	0.15–1.4
GA			2.19	0.72–6.7
AA			-	-

Note: AH – arterial hypertension; TTH – tension-type headache. The genotype homozygous for the recessive allele (AA) was not found in the study sample.

At the same time, significant differences in frequencies of rs7314935 alleles and genotype were shown in comparing group 1 (main subgroup – AH+TTH) versus group 2 (control) (see Figure 2, table 4). Thus, in comparing allele frequencies (see Figure 2(a), table 4), the differences tended to the level of significance (p=0.057). The minor allele A was 2.47 times more common in group 1 (main subgroup – AH+TTH) compared with group 2 (control): 20.0% versus 8.1%. In comparing genotype frequencies (see Figure 2(b), table 4), the difference reached statistical significance (p=0.038). The heterozygous genotype GA was 2.48 times more common in group 1 (main subgroup – AH+TTH) compared with group 2 (control): 40.0% versus 16.1%.

The GA genotype was associated with a triple risk of the «AH+TTH» phenotype development compared with group 2 (control): (OR=3.47 [95% CI: 1.04–11.56], p=0.038). However, the heterozygous genotype rs7314935 did not significantly affect the risk of AH development (OR=2.541 [95% CI: 0.8–7.25], p=0.111) in the Caucasian Siberian population.

Patients with clinical phenotypes may have two and more diseases. Thus, clinical phenotypes are very diverse and heterogeneous because there are many possible relationships between different diagnoses, as well as their clinical and genetic features. A phenotype is a condition in which a patient has signs of at least two diseases that have a common clinical picture and pathophysiology. Since TTH and headache in AH (headache associated with homeostasis disorders) have such common features, the probability of diagnostic difficulties is very high and the frequency of this phenotype development in the clinical

practice of neurologists and therapists is also very high. In addition, we previously demonstrated the role of NO and nNOS in this condition [12, 23].

So, nNOS is expressed in the cerebrovascular system, cardiovascular system and skeletal muscles (see Figure 2) [18] and, in addition to NO, generates H_2O_2 [24]. In general, the complex two-domain structure of nNOS has a deep correlation with cardiovascular and cerebrovascular disorders [7]. It is assumed that nNOS contributes to the control of blood pressure, cerebral blood flow and tone of pericranial skeletal muscles in healthy subjects [23]. In addition, there are hypotheses that nNOS can contribute to the control of vascular and pericranial skeletal muscle relaxation in patients with AH and TTH undergoing medication [23]. Selective blockade of nNOS can reduce the degree of vasorelaxation and muscle relaxation. However, this inhibitory effect is higher in patients with controlled AH. It is interesting that the expression of nNOS is higher in pharm-controlled hypertensive patients than in patients with uncontrolled AH and normotensive patients [24].

It is also known that the expression level of nNOS is genetically predetermined. The *NOS1* gene encoding nNOS is located on chromosome 12 in humans (see Figure 1) [15, 16]. Mutations and SNPs in the *NOS1* gene can significantly alter the expression of this enzyme and the production of NO, both in clinically healthy individuals and in patients with AH+TTH. Transcript variants (difference in 5'UTR) for *NOS1* gene are described but poorly studied. In addition, alternatively spliced transcript variants have been found for this gene [25].

We analysed the scientific literature describing rs7314935 (117718837 G>A) as a genetic biomarker of AH and primary headache (including TTH). Papers aimed at finding the association of rs7314935 with the phenotype were not found.

Most of the associative genetic studies of rs7314935 with primary headaches were carried out on the example of patients with migraine, which has pathogenetic mechanisms different from TTH. Thus, no associations of this SNP with a high risk of developing migraine were found in Japanese (Ishii M. et al. (2014) [26]) and Spanish (García-Martín E. et al. (2019) [27]) populations. According to our analysis, the role of rs7314935 as a genetic biomarker of TTH has not been previously studied. In addition, rs7314935 of the *NOS1* gene has been studied as a genetic biomarker of the AH. Thus, Levinsson A. et al. (2014) showed on the example of the Swedish population that the carriage of the homozygous recessive genotype AA rs7314935 increases this risk (OR=2.15; 95% CI 1.06–4.37, p=0.03) [28].

Conclusion

Our study was shown that the heterozygous genotype GA of rs7314935 of the *NOS1* gene may be new genetic biomarker of «AH+TTH» phenotype developing in Caucasian hypertensive patients from East Siberia.

References

1. Russian Society of Cardiology. Arterial hypertension in adults: Clinical guidelines 2022. (In Russian). Accessed July 01, 2023. https://cr.minzdrav.gov.ru/recomend/62_2

2. Russian Society of Neurologists. Russian Headache Society. Tension-type headache (TTH) in adults: Clinical guidelines 2021. (In Russian). Accessed July 01, 2023. https://cr.minzdrav.gov.ru/recomend/162_2

3. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. NCD Risk Factor Collaboration (NCD-RisC). *Lancet (London, England)*. 2021;398(10304):957-80. DOI:10.1016/S0140-6736(21)01330-1

4. Al Jumah M, Al Khathaami AM, Kojan S, Hussain M, Thomas H, Steiner TJ. The prevalence of primary headache disorders in Saudi Arabia: a cross-sectional population-based study. *The Journal of Headache And Pain*. 2020;21(1):11. DOI:10.1186/s10194-020-1081-1

5. Токарь ОО, Жмеренецкий КВ, Заднепровская ВВ, Неврычева ЕВ. Оценка экстракраниального и интракраниального артериального кровообращения у пациентов молодого возраста с артериальной гипертонией, сопровождающейся мигренью или головной болью напряжения. *Дальневосточный медицинский журнал*. 2020;(1):28-36. [Tokar' OO, Zhmereneckij KV, Zadneprovskaya VV, Nevrycheva EV. Evaluation of extracranial and intracranial arterial blood flow in young patients with arterial hypertension associated with migraine or tension-type headache. *Far Eastern Medical Journal (Dal'nevostochnyj Medicinskij Zhurnal)*. 2020;(1):28-36. (In Russian)]. DOI:10.35177/1994-5191-2020-1-28-36

6. Rajapakse NW, Giam B, Kuruppu S, Head GA, Kaye DM. Impaired L-arginine-nitric oxide pathway contributes to the pathogenesis of resistant hypertension. *Clinical Science (London, England:1979)*. 2019;133(20):2061-2067. DOI:10.1042/cs20190851

7. Kurkin DV, Abrosimova EE, Bakulin DA, Kovalev NS, Dubrovina MA, Borisov AV, Strygin AV, Morkovin EI, Tyurenkov IN. Activity modulation of various nitric oxide syntases as an approach to endothelial dysfunction therapy. *Pharmacy & Pharmacology*. 2022;10(2):130-153. (In Russian). DOI:10.19163/2307-9266-2022-10-2-130-153

8. Morozova NI, Mulerova TA, Tsygankova DP, Indukaeva EV, Bazdyrev ED, Nahratova OV, Ogarkov MYu. Factors predisposing to carotid atherosclerosis progression in patients with arterial hypertension. *Siberian Medical Review*. (In Russian). 2022;(1):37-44. DOI: 10.20333/25000136-2022-1-37-44

9. Steel SJ, Robertson CE, Whealy MA. Current Understanding of the Pathophysiology and Approach to Tension-Type Headache. *Current Neurology And Neuroscience Reports*. 2021;21(10):56. DOI:10.1007/s11910-021-01138-7

10. de Heus RAA, Reumers SFI, van der Have A, Tumelaire M, Tully PJ, Claassen JAHR. Day-to-Day Home Blood Pressure Variability is Associated with Cerebral Small Vessel Disease Burden in a Memory Clinic Population. *J Alzheimers Dis*. 2020;74(2):463-472. Doi:10.3233/JAD-191134

11. Chong CM, Ai N, Ke M, Tan Y, Huang Z, Li Y, Lu JH, Ge W, Su H. Roles of Nitric Oxide Synthase Isoforms in Neurogenesis. *Molecular Neurobiology*. 2018;55(3):2645-2652. DOI:10.1007/s12035-017-0513-7

12. Shnayder NA, Petrova MM, Moskaleva PV, Shesternya PA, Pozhilenkova EA, Nasyrova RF. The role of single-nucleotide variants of NOS1, NOS2, and NOS3 genes in the comorbidity of arterial hypertension and tension-type headache.

*Molecules (Basel, Switzerland).*2021;26(6):1556. DOI:10.3390/molecules26061556

13. Do TP, Heldarskard GF, Kolding LT, Hvedstrup J, Schytz HW. Myofascial trigger points in migraine and tension-type headache. *The Journal of Headache And Pain*. 2018;19(1):84. DOI:10.1186/s10194-018-0913-8

14. Tully PJ, Yano Y, Launer LJ, Kario K, Nagai M, Mooijaart SP, Claassen JAHR, Lattanzi S, Vincent AD, Tzourio C; Variability in Blood Pressure and Brain Health Consortium; Variability in Blood Pressure and Brain Health Consortium. Association between blood pressure variability and cerebral small-vessel disease: a systematic review and meta-analysis. *Journal of The American Heart Association*. 2020;9(1):e013841. DOI:10.1161/JAHA.119.013841

15. Gene Cards. The Human Gene Database. NOS1 gene. Accessed July 01, 2023. https://www.genecards.org/cgi-bin/carddisp.pl?gene=NOS1

16. Su AI, Wiltshire T, Batalov S, Lapp H, Ching KA, Block D, Zhang J, Soden R, Hayakawa M, Kreiman G, Cooke MP, Walker JR, Hogenesch JB. A gene atlas of the mouse and human protein-encoding transcriptomes. *Proceedings of the National Academy of Sciences of the United States of America.* 2004;101(16):6062–6067. DOI:10.1073/pnas.0400782101

17. National Library of Medicine. NCBI (National Center for Biotechnology information). SNP DB (Single Nucleotide Polymorphisms' Data Base). rs7314935. Accessed July 01, 2023. https://www.ncbi.nlm.nih.gov/snp/?term=7314935

18. The Human Protein Atlas. Tissue Cell Type. NOS1 gene. Accessed July 01, 2023. https://www.proteinatlas.org/ENSG00000089250-NOS1/tissue

19. Geography of Genetic Variants Browser. rs7314935. Accessed July 01, 2023. https://popgen.uchicago.edu/ggv/?data=%221000genomes%22&chr=12&pos=117718837

20. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *Journal of Hypertension.* 2018;36(10):1953-2041. DOI:10.1097/HJH.0000000000001940

21. Kobalava ZD, Konradi AO, Nedogoda SV, Shlyakhto EV, Arutyunov GP, Baranova EI, Barbarash OL, Boitsov SA, Vavilova TV, Villevalde SV, Galyavich AS, Glezer MG, Grineva EN, Grinstein YuI, Drapkina OM, Zhernakova YuV, Zvartau NE, Kislyak OA, Koziolova NA, Kosmacheva ED, Kotovskaya YuV, Libis RA, Lopatin YuM, Nebiridze DV, Nedoshivin AO, Ostroumova OD, Oschepkova EV, Ratova LG, Skibitsky VV, Tkacheva ON, Chazova IE, Chesnikova AI, Chumakova GA, Shalnova SA, Shestakova MV, Yakushin SS, Yanishevsky SN. Arterial hypertension in adults. Clinical guidelines 2020. *Russian Journal of Cardiology.* 2020;25:3786. (In Russian). DOI:10.15829/1560-4071-2020-3-3786

22. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. 2018;38(1):1-211. DOI:10.1177/0333102417738202

23. Alyabyeva PV, Chastina OV, Petrova MM, Lareva NV, Garganeeva NP, Chumakova GA, Cherniaeva MS, Shnayder NA. New genetic biomarkers of the overlap syndrome tension-type headache and arterial hypertension. *Genes.* 2022;13(10):1823. DOI:10.3390/genes13101823

24. Costa ED, Silva JF, Aires RD, Garcia DC, Kansaon MJ, Wainstein AJ, Rezende BA, Teixeira MM, Silva RF, Cortes SF, Lemos VS. Neuronal nitric oxide synthase contributes to the normalization of blood pressure in medicated hypertensive patients. *Nitric Oxide : Biology And Chemistry*. 2018;(80):98-107. DOI:10.1016/j.niox.2018.09.003

25. Rouillard AD, Gundersen GW, Fernandez NF, Wang Z, Monteiro CD, McDermott MG, Ma'ayan A. The harmonizome: a collection of processed datasets gathered to serve and mine knowledge about genes and proteins. *Database: The Journal Of Biological Databases And Curation.* 2016;2016:baw100. DOI:10.1093/database/baw100.

26. Ishii M, Yahara M, Katoh H, Kawamura M, Shimizu S. Polymorphisms of nitric oxide synthase and GTP cyclohy-drolase I genes in Japanese patients with medication overuse headaches. *American Journal Of Rhinology and Allergy.* 2014;19(3):277–281

27. García-Martín E, Martinez C, Serrador M, Alonso-Navarro H, Navacerrada F, García-Albea E, Agundez JA, Jiménez-Jiménez FJ. Neuronal Nitric Oxide Synthase(nNOS, NOS1) rs693534 and rs7977109 Variants and Risk for Migraine. *Headache The Journal Of Head And Face Pain*. 2015;(55):1209–1217. DOI:10.1111/head.12617

28. Levinsson A, Olin A-C, Björck L, Rosengren A, Nyberg F. Nitric oxide synthase (NOS) single nucleotide polymorphisms are associated with coronary heart disease and hypertension in the INTERGENE study. *Nitric Oxide: Biology And Chemistry.* 2014;(39):1-7. DOI:10.1016/j.niox.2014.03.164

Author information

Marina M. Petrova, Dr.Med.Sci., Prof., Prof. V. F. Voino-Yasenetsky Krasnoyarsk State Medical University; Address: 1, Partizan Zheleznyak Str., Krasnoyarsk, Russian Federation 660022; Phone: +7(391)2280628; e-mail: stk99@yandex.ru, http://orcid.org/0000-0002-8493-0058

Polina A. Reznichenko, Student, Prof. V. F. Voino-Yasenetsky Krasnoyarsk State Medical University; Address: 1, Partizan Zheleznyak Str., Krasnoyarsk, Russian Federation 660022; Phone: +7(913)0440045; e-mail: polina.reznichenko.98@mail.ru, http://orcid.org/0000-0002-5965-4362

Polina V. Alyabyeva, Graduate Student, Prof. V. F. Voino-Yasenetsky Krasnoyarsk State Medical University; Address: 1, Partizan Zheleznyak Str., Krasnoyarsk, Russian Federation 660022; Phone: +7(983)1470361; e-mail: polina-moscaleva@yandex.ru, http://orcid.org/0000-0002-8833-1052

Irina V. Romanova, Ph.D.Med.Sci., Associate Prof., Prof. V. F. Voino-Yasenetsky Krasnoyarsk State Medical University; Address: 1, Partizan Zheleznyak Str., Krasnoyarsk, Russian Federation 660022; Phone: +7(913)5137365; e-mail: irinavr2018@gmail.com, http://orcid.org/0000-0003-1299-3233

Regina F. Nasyrova, Dr.Med.Sci., Psychiatrics, Clinical Pharmacologist, General Researcher of the Center of Personalized Psychiatry and Neurology; V.M. Bekhterev National Medical Research Center of Psychiatry and Neurology; Address: 3, Bekhterev str., St Petersburg, Russian Federation 192019; Phone: +7(812)6700220 7813; e-mail: nreginaf77@gmail.com, http://orcid.org/0000-0003-1874-9434

Natalia A. Shnayder, Dr.Med.Sci., Prof., Neurologist, Leading Researcher of the Center of Personalized Psychiatry and Neurology; V.M. Bekhterev National Medical Research Center of Psychiatry and Neurology; Address: 3, Bekhterev str., St Petersburg, Russian Federation 192019; Phone: +7(812)6700220 7814; Leading Researcher of the Center for Collective Use «Molecular and Cellular Technologies»; Prof. V. F. Voyno-Yasenetsky Krasnoyarsk State Medical University; Address: Address: 1, Partizan Zheleznyak Str., Krasnoyarsk, Russian Federation 660022; e-mail: nataliashnayder@gmail.com, http://orcid.org/ 0000-0002-2840-837X

Received 03 April 2023
Revision Received 30 August 2023
Accepted 28 September 2023