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Clinical and Genetic Features of Uncontrolled, Complicated Arterial Hypertension in Hypertensive Patients of the Aral Sea Region

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Abstract

The purpose of this study was to assess the clinical and genetic features of the course of hypertension, complicated by a hypertensive crisis in the inhabitants of the Aral Sea region.

Methods and Results: The study included 132 patients (52 men and 80 women) with AH who applied at least 5 times (4.9±2.4) during 1 year to the Nukus Emergency Medical Care Center with a diagnosis of "Uncomplicated hypertensive crisis." The mean age of the patients was 57.2±11.6 years, the mean duration of AH – 8.85±3.4 years. The control group consisted of 50 healthy people (mean age of 52.7±6.4 years), women and men in equal proportions. A cardio Hypertension Panel of multiplex RT-PCR assay was used to detect 4 SNP [*ADD1* rs4961 (G460T), *GNB3* rs5443 (C825T), *AGT* rs4762 (C521T), and *AGT* rs699 (T704C)]. To assess the strength of the association between a genetic marker and AH, measured by the OR, we used multiplicative and additive models.

According to the results of office BP measurement, the average SBP corresponded to AH Grade 3 (200.8±22.6 mmHg), and DBP corresponded to AH Grade 2 (105.4±7.62 mmHg). All AH patients, regardless of gender, were diagnosed with left ventricular hypertrophy and increased carotid intima-media thickness. Microalbuminuria was detected in 89 (67.4%) patients, proteinuria in 39 (29.6%) patients. Among AH patients, 88% had a high salt taste sensitivity threshold (STST) and 12% had a medium STST (χ^2=269.455, *P*=0.0001). Analysis of the multiplicative and additive models for the *AGT* rs699 (T704C) SNP showed a significant risk of AH with the carriage of the T allele (OR=3.70, 95% CI: 1.88-7.26, *P*=0.000) and the homozygous TT genotype and heterozygous CT genotype (OR=12.55, 95% CI: 0.72-218.80, *P*=0.000, and OR=2.67, 95% CI: 1.24-5.74, *P*=0.000, respectively). At the same time, the carriage of the C allele and CC genotype may be protective against the development of AH in individuals of the Aral Sea region. Analyzing the additive models, we also found a significant risk of AH with the carriage of the homozygous CC genotype of the *AGT* rs4762 (C521T) SNP (OR=5.92, 95% CI: 2.78-12.63, *P*=0.000). For the *ADD1* rs4961 (G460T) SNP and the *GNB3* rs5443 (C825T) SNP, we did not find associations with the risk of AH. The presence of ethnic differences in the prevalence and associative links of AH candidate genes with the development of the salt-sensitivity phenotype require further extended searches in this direction, especially in the Aral Sea region.(**International Journal of Biomedicine. 2022;12(3):360-366.**).

Keywords: arterial hypertension • salt sensitivity • Aral Sea • candidate genes

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Abbreviations

AH, arterial hypertension; **AHT**, antihypertensive therapy; **AGT**, angiotensinogen; **ACEIs**, angiotensin-converting enzyme inhibitors; **ARBs**, angiotensin receptor blockers; **BP**, blood pressure; **CIMT**, carotid intima-media thickness; **CCBs**, calcium channel blockers; **DBP**, diastolic BP; e**GFR**, estimated glomerular filtration rate; **HWE**, Hardy–Weinberg equilibrium; **LVH**, left ventricular hypertrophy; **LVMI**, left ventricular mass index; **MAU**, microalbuminuria; **RAAS**, renin-angiotensin-aldosterone system; **SBP**, systolic BP; **SSH**, salt-sensitive hypertension; **STST**, the salt taste sensitivity threshold.

Introduction

The disappearance of the Aral Sea is an ecological catastrophe of our time.[1] The Aral Sea was the fourth largest lake in the world by water surface area in 1960. Water withdrawal for irrigation was a primary reason for the desiccation of the lake. The Aral Sea surface area has declined from 68,000 km^2 in 1960 to 14,280 km^2 in 2010, water volume reduced from 1,093.0 km^3 in 1960 to 98.1 km^3 in 2010, and salinity increased from 10 g/L in 1960 to 130 g/L in 2010.[2] Local climate change has occurred simultaneously with the disappearance of water. An arid, sharply continental climate in the Aral Sea basin, a high salinity level, pollution, and lack of drinking water, all of which are harmful to human health. [1] More than one generation has already changed, struggling with this environmental catastrophe, which undoubtedly has affected the health of the population of the Aral Sea region, and in particular, the phenotype of arterial hypertension (AH).

According to the STEPS study, conducted in Uzbekistan in 2019, the prevalence of hypertension among the adult population aged 18-69 years was 38%; 34.4% of respondents had high salt intake, according to their response to the following item on the questionnaire: "always or often add salt, salty sauces or savory gravies before or during meals"; and one sixth of the population ate less than 5 servings of vegetables and/or fruits per day, on average. Patients with hypertension in the Aral Sea zone are subject to both climatic and environmental impacts, as well as the impact of high blood pressure (BP) on target organs and cardiovascular risk. At the same time, despite the widespread clinical introduction of combined antihypertensive therapy, in some patients it is not possible to control BP and achieve the target level. Patients with uncontrolled hypertension have a worse prognosis for both cardiovascular events and the development of complications in the form of hypertensive crises. It should be noted that properly selected, rational antihypertensive therapy, patients' adherence to treatment and adherence to a healthy lifestyle— in particular, reducing the amount of NaCl consumed to the WHO recommended <5g/day— contribute to the control of BP. The significance of high salt intake and the development of salt-sensitive hypertension (SSH) was previously noted in our earlier publications.

AH is a complex trait determined by both genetic and environmental factors. To date, more than 90 different genetic polymorphisms that appear to be associated with high BP have been identified.[3] Most interest in the genetic polymorphisms linked to SSH has focused on the genes involved in sodium transport (*NKCC1*), genes involved in regulating the RAAS (*AGT, ACE*), and the *ADD*1 and *CNB3* genes.

The purpose of our study was to assess the clinical and genetic features of the course of hypertension, complicated by a hypertensive crisis in the inhabitants of the Aral Sea region.

Materials and Methods

The study included 132 patients (52 men and 80 women) with AH who applied at least 5 times (4.9±2.4) during 1 year to the Nukus Emergency Medical Care Center with a diagnosis of "Uncomplicated hypertensive crisis." The mean age of the patients was 57.2±11.6 years, the mean duration of AH – 8.85±3.4 years. Exclusion criteria were complicated hypertensive crisis, acute coronary syndrome, acute cerebrovascular accident, exfoliating aortic aneurysm, severe co-morbid conditions, cardiac arrhythmias, chronic heart failure (NYHA FC>III) in the stage of decompensation.

Examination of AH patients with uncomplicated hypertensive crises was carried out within 10-15 minutes of admission, according to the recommendations of the ESC/ESH (2018).[4] Emergency care included captopril 25–50 mg SL or urapidil 5–10 mg IV bolus.

All patients underwent the following examinations: assessment of traditional risk factors, physical examination, clinical and biochemical laboratory methods, 12-lead ECG, and echocardiography. Office BP was measured using a mercury sphygmomanometer, according to Korotkov's method. BP was measured 3 times, and the means of these measurements were used in the analyses.

Echocardiography was carried out according to the recommendations of the American Society of Echocardiography in M- and B-modes using Philips EnVisor C Ultrasound Machine (the Netherlands). Left ventricular hypertrophy (LVH) was defined as LVMI of >95 g/m^2 (for women) and >115 g/m^2 (for men).[4] CCA IMC thickness was assessed for both left and right carotid arteries using a 7.5 MHz linear array transducer (Sonoline Versa Pro ultrasound system, Siemens, Germany).

The salt taste sensitivity threshold (STST) was assessed according to the method of R. Henkin.[5] The level of MAU (albumin in *24-hour urine* between 30-300 mg) was determined by the enzymatic method, using the biochemical analyzer Daytona TM (Rendox, Great Britain).

The genetic part of the study included 96 AH patients (56 women and 40 men) with uncomplicated hypertensive crisis and mean age of 55.3±8.6 years. The control group consisted of 50 healthy people (mean age of 52.7±6.4 years), women and men in equal proportions.

Genomic DNA samples were isolated from the peripheral blood leukocytes by using the PROBA-RAPID kit according to manufacturer`s protocol. A cardio Hypertension Panel of multiplex RT-PCR assay was used to detect 4 SNP [*ADD1* rs4961 (G460T), *GNB3* rs5443 (C825T), *AGT* rs4762 (C521T), and *AGT* rs699 (T704C)].

Statistical analysis was performed using the statistical software «Statistica». (v10.0, StatSoft, USA). The normality of distribution of continuous variables was tested by one-sample Kolmogorov-Smirnov test. For descriptive analysis, results are presented as mean±standard deviation (SD), median, interquartile range (IQR; Q1 to Q3). Means of 2 continuous normally distributed variables were compared by independent samples Student's t test. The Mann-Whitney U Test was used to compare the differences between the two independent groups (for nonparametric data). Group comparisons with respect to categorical variables were performed using chi-square test. A probability value of $P<0.05$ was considered statistically significant. Genetic markers for HWE were tested. Differences in the allele and genotype distribution between the groups were

assessed by χ2- test with Yates correction or Fisher's exact test, when appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Two genetic models were analyzed: the additive inheritance model (Cochran-Armitage Linear Trend Test) and the multiplicative inheritance model.

The study protocol was reviewed and approved by the Ethics Committee of the Republican Specialized Centre of Cardiology. All participants provided the written informed consent.

Results

According to the results of office BP measurement, the average SBP corresponded to AH Grade 3 (200.8±22.6 mmHg), and DBP corresponded to AH Grade 2 (105.4±7.62 mmHg). Heart rate was 79.86±11.54 bpm. About 86% of patients were diagnosed with obesity degree 1-2 (BMI 30.2±4.78 kg/m²), and 30.3% of patients with coronary artery disease FC I-II. A history of MI was found in 8.3% of patients, Type 2 diabetes mellitus in 19.5% of cases, and the consequences of a stroke 6 months prior in 6.06% of cases. Analysis of the survey of previous therapy showed that 41(31%) patients were not treated, although they previously knew about the increase in BP; 79(60%) patients received only one antihypertensive medication, of which more than half were treated with RAAS blockers; and the rest of the patients were equally treated with beta-blockers and BCCs. Dual AHT was noted in 10(7.5%) patients and triple AHT in 2 patients. A diuretic was included in combined AHT only in 1 case. Thus, patients with uncontrolled hypertension did not receive proper AHT, and one third of patients did not take antihypertensive medication, which was the reason for the development of the uncomplicated hypertensive crisis.

All AH patients, regardless of gender, were diagnosed with LVH and increased CIMT. MAU was detected in 89(67.4%) patients, proteinuria in 39(29.6%) patients. Thus, in our AH patients, the presence of multiple hypertension-mediated organ damage (LVH, vascular and renal damage) was revealed against the background of uncontrolled hypertension (Table 1), which indicates a high and high-to-very-high cardiovascular risk.

Among AH patients, 88% had a high STST and 12% had a medium STST (χ^2=269.455, *P*=0.0001). In the control group, there were persons with low, medium, and high STST, while persons with medium and high STST accounted for 70% (χ^2=0.78 *P*=0.677). However, there were significant intergroup differences in reaching the threshold concentration of NaCl and in the amount of sodium ions excreted in the urine, which indicates a greater intake of dietary sodium in AH patients and characterizes hypertension as SSH.

The case-control design is often employed for testing the association between a marker and a disease. In a case-control study, the strength of an association is measured by the odds ratio (OR). Given 2 alleles (A, a) of an SNP, the 3 possible genotypes (AA, Aa, aa) can be dichotomized in different ways yielding different genetic models.[6] In our study, we used multiplicative (A vs. a) and additive (AA vs. aa, AA vs. Aa, and Aa vs. aa) models.

Table 1.

Markers of target organ damage and STST data in AH patients and controls

Variable	AH patients (n=132)	Control group (n=50)	*P*
LVMI, g/m²	171.62±30.9	82.2±20.1	0.000
CIMT, mm	1.24±0.16	0.8±0.1	0.000
MAU, mg/24-h	221.0±130.2	19.4±5.2	0.000
eGFR mL/min/1.73m²	65.2±18.8	101.4±8.5	0.000
NaCl,% (Henkin test)	0.48±0.22% 0.64 [0.32; 0.64]	0.21±0.14 0.16 [0.08; 0.32]	0.000
Na^+ in daily urine, mmol/L	162.4±42.8 166.4 [133.5; 202.4]	121.9±42.3 129.6 [85.2; 158.8]	0.000

The HWE plays an important role in genetic epidemiologic studies. If the controls are in HWE, the cases may then be tested. There are many factors that can result in deviation from HWE, such as a genotyping error, population stratification, and so on [7-10]. If the cases are in HWE, the data may be analyzed by allele counting, as any genetic effect is consistent with a multiplicative model.[11] In the absence of HWE in controls, the allelic association test is not suitable and alternative methods must be used to test for multiplicative models.[12] The Cochran–Armitage trend test (CATT),[13,14] which utilizes an additive model, is usually more powerful than Pearson's chi-squared test with 2df.[15]

The distribution of polymorphic markers of the *ADD1* rs4961 (G460T), *GNB3* rs5443 (C825T), *AGT* rs4762 (C521T), and *AGT* rs699 (T704C) is presented in Table 2.

The distribution of polymorphic markers of the *ADD*1 rs4961 (G460T) SNP in AH patients and controls was in HWE. An analysis of the frequency distribution of alleles of the *ADD1* rs4961 (G460T) showed that the carriage of the G allele was dominant in AH patients (65.4% vs. 34.6% for the T allele; χ^2=35.787, *P*=0.000) and controls (66% vs. 34% for the T allele; χ^2=20.48, *P*=0.000). In AH patients and controls, the genotype distribution was as follows: GG=40.4%, GT=50%, TT=9.6% (χ2=37.755, *P*=0.000) and GG=44%, GT=44%, TT=12% (χ2=15.36, *P*=0.001), respectively.

The distribution of polymorphic markers of the *GNB3* rs5443 (C825T) SNP in controls was in HWE. We found HWE was absent in AH patients**.** An analysis of the frequency distribution of alleles of the *GNB3* rs5443 (C825T) SNP showed that the carriage of the C allele was dominant in AH patients (67.6% vs. 32.4% for the T allele; χ^2=46.34, *P*=0.000) and controls (65% vs. 35% for the T allele; χ^2=18.0, *P*=0.000). In AH patients and controls, the genotype distribution was as follows: CC=39.4%, CT=56.4%, TT=4.2% (χ^2=59.77, *P*=0.000) and CC=42%, CT=46%, TT=12% (χ^2=15.54, *P*=0.000), respectively.

The distribution of polymorphic markers of the *AGT* rs4762 (C521T) SNP in controls was not in HWE. An analysis of the frequency distribution of alleles of the *AGT*

rs4762 (C521T) showed that the carriage of the C allele was dominant in both AH patients (87.8% vs. 12.2% for the T allele; χ^2=214.5, *P*=0.000) and controls (70% vs. 30% for the T allele; χ^2=32.0, *P*=0.000.). In AH patients and controls, the genotype distribution was as follows: CC=79.8%, CT=16%, TT=4.2% (χ^2=139.8, *P*=0.000) and CC=40%, CT=60%, TT=0 (χ^2=42.0, *P*=0.000), respectively. Thus, we revealed a significant predominance of the homozygous CC genotype in patients and the heterozygous CT genotype in controls in the absence of the homozygous TT genotype.

The distribution of polymorphic markers of the *AGT* rs699 (T704C) SNP in AH patients and controls was in HWE. An analysis of the frequency distribution of alleles of the *AGT* rs699 (T704C) SNP showed that the carriage of the C allele was dominant in both AH patients (66.5% vs. 33.5% for the T allele; χ^2=40.894, *P*=0.000) and controls (88% vs. 12% for the T allele; χ^2=115.52, *P*=0.000). In AH patients and controls, the genotype distribution was as follows: CC=43.6%, CT=45.8%, TT=10.6% (χ^2=32.777, *P*=0.000) and CC=76%, CT=24%, TT=0 (χ^2=67.92, *P*=0.000), respectively. Thus, in contrast to AH patients, the homozygous CC genotype was dominant in healthy individuals.

To assess the strength of the association between a genetic marker and AH, measured by the OR, we used multiplicative (Table 3) and additive (Table 4) models. Taking into account the absence of HWE in controls for the *AGT* rs4762 (C521T) SNP, the multiplicative model was excluded in this case.

Analysis of the multiplicative and additive models for the *AGT* rs699 (T704C) SNP showed a significant risk of AH with the carriage of the T allele (OR=3.70, 95% CI: 1.88-7.26, *P*=0.000) and the homozygous TT genotype and heterozygous CT genotype (OR=12.55, 95% CI: 0.72-218.80, *P*=0.000, and OR=2.67, 95% CI: 1.24-5.74, *P*=0.000, respectively). At the same time, the carriage of the C allele and CC genotype may be protective against the development of AH in individuals of the Aral Sea region.

Analyzing the additive models, we also found a significant risk of AH with the carriage of the homozygous CC genotype of the *AGT* rs4762 (C521T) SNP (OR=5.92, 95% CI: 2.78-12.63, *P*=0.000). For the *ADD1* rs4961 (G460T) SNP and the *GNB3* rs5443 (C825T) SNP, we did not find associations with the risk of AH.

Table 3.

Genetic predisposition to AH (the multiplicative inheritance model)

Gene	SNP	Allele	Frequency of alleles		χ^2	*P*	OR (95% CI)
			AH	Control			
ADD1	rs4961 G460T	G	0.654	0.660	0.01	0.996	0.97 (0.58-1.63)
		T	0.346	0.340			1.03 (0.62-1.71)
GNB3	rs5443 C825T	C	0.68	0.65	0.19	0.909	1.12 (0.67-1.87)
		T	0.32	0.35			0.89 (0.53-1.49)
AGT	rs699 T704C	C	0.665	0.88	15.68	0.000	0.27 (0.14-0.53)
		T	0.335	0.12			3.70 (1.88-7.26)

Table 2.

The distribution of polymorphic markers of the ADD1 rs4961 (G460T), GNB3 rs5443 (C825T), AGT rs4762 (C521T), and AGT rs699 (T704C) in AH patients and controls.

Gene	SNP	Genotype	AH	HWE	χ^2	*P*	Control	HWE	χ^2	*P*	Allele	Frequency of alleles	
												AH	Control
ADD1	rs4961 G460T	GG	0.404	0.428	1.040	0.5945	0.440	0.436	0.019	0.9904	G	0.654	0.66
		GT	0.500	0.452			0.440	0.449			T	0.346	0.34
		TT	0.096	0.120			0.120	0.116					
GNB3	rs5443 C825T	CC	0.394	0.456	7.698	0.0213	0.420	0.423	0.006	0.9970	C	0.68	0.65
		CT	0.564	0.438			0.460	0.455			T	0.32	0.35
		TT	0.043	0.105			0.120	0.123					
AGT	rs4762 C521T	CC	0.798	0.770	6.205	0.0449	0.400	0.490	9.184	0.0101	C	0.878	0.70
		CT	0.160	0.215			0.600	0.420			T	0.122	0.30
		TT	0.042	0.015			0.000	0.090					
AGT	rs699 T704C	CC	0.436	0.442	0.066	0.9674	0.760	0.774	0.93	0.6282	C	0.665	0.88
		CT	0.457	0.446			0.240	0.211			T	0.335	0.12
		TT	0.106	0.112			0.000	0.014					

Table 4.

Genetic predisposition to AH (the additive inheritance model [CATT])

Gene	SNP	Genotype	AH	Control	χ^2	*P*	OR (95% CI)
ADD1	rs4961 G460T	GG	0.40	0.44	0.01	0.995	0.86 (0.43-1.73)
		GT	0.50	0.44			1.27 (0.64-2.54)
		TT	0.10	0.12			0.78 (0.26-2.32)
GNB3	rs5443 C825T	CC	0.394	0.42	0.16	0.924	0.896 (0.45-1.80)
		CT	0.564	0.46			1.52 (0.76-3.02)
		TT	0.042	0.12			0.33 (0.09-1.21)
AGT	rs4762 C521T	CC	0.798	0.400	14.30	0.000	5.92 (2.78-12.63)
		CT	0.160	0.600			0.13 (0.06-0.28)
		TT	0.043	0.000			5.02 (0.26-95.19)
AGT	rs699 T704C	CC	0.436	0.76	10.57	0.005	0.24 (0.11-0.53)
		CT	0.458	0.24			2.67 (1.24-5.74)
		TT	0.106	0.00			12.55 (0.72-218.80)

Discussion

As is known, environmental conditions play an important role in the mechanisms of development of salt-sensitive hypertension. In the Aral Sea region, they are extremely unfavorable in terms of salinity of the soil and water, which, of course, leads to excessive consumption of sodium chloride. Apparently, the increased consumption of sodium chloride in the Aral Sea region leads to a large amount of SSH and a complicated course of the disease. However, until now, it remains unclear in whom and to what extent excessive consumption of sodium chloride has a pathological effect on the level of BP. It is known that among those who take a significant amount of salt with food, AH does not develop in all cases. And vice versa, as practice shows, restriction of salt intake does not always lead to a significant decrease in BP of AH patients. In this regard, it is suggested that sodium chloride has a significant effect on the regulation of BP only in individuals with a certain hereditary background.

In a number of works,[16,17] not only an increase in STST in essential hypertension was noted, but also its genetic determination in families of AH patients. Thus, in the Rostov population, the hereditary predisposition to AH was determined by the coefficient of heritability of STST, which amounted to 0.425 ($P<0.05$),[16] i.e. the genetic variability of STST was determined by 42.5%, while the phenotypic variability was determined by 57.5%, which justifies the need for preventive measures (restriction of dietary sodium intake) among healthy relatives of AH patients.

Individual components of the RAAS also predispose people to the formation of increased salt sensitivity.[18] The presence of a genetic predisposition to salt sensitivity is evidenced by the results of observing Kuna Indians, who lived in isolation on the San Blas Islands for a long time and, therefore, consumed practically no salt. Over the past 50 years, the diet of many of them began to contain the same amount of sodium as that of the inhabitants of nearby Panama, but, unlike the latter, their BP remains stably normal.[19]

Salt sensitivity is estimated to be present in 51% of the hypertensive and 26% of the normotensive populations.[18] The individual blood pressure response to salt is heterogeneous and possibly related to inherited susceptibility. Previous family studies have documented a moderate to high heritability of salt sensitivity, generally ranging from 22% to 84%.[20-22] Linkage analyses and genetic association studies have suggested that genetic mechanisms may play a pivotal role in BP salt sensitivity.[23] A number of genes that predispose one to salt sensitivity have already been established in humans.[24-31]

Liu et al.[32] conducted a meta-analysis of 22 studies including 14,303 hypertensive patients and 15,961 normotensive patients, which demonstrated a significantly insignificant association of the T allele of the *ADD1* G460T SNP with the risk of developing AH, compared with the G allele (P=0.69, OR=1.02, 95% CI: 0.94-1.10, P heterogeneity<0.0001). Meta-analysis conducted on other genetic traits also did not reveal significant differences in the general population, as in Caucasians, East Asians and other populations. Thus, the conducted meta-analysis did not prove the association of the *ADD1* G460T SNP with AH.

In a study by Marlin,[33] an increase in serum sodium levels with a simultaneous decrease in potassium concentration was observed in the presence of the TT variant of the *GNB3* rs5443 (C825T) SNP, which contributes to a significant increase in the activity of the renal Na+/H+ transporter. Thus, the products of most of the genes involved in the development of salt sensitivity, one way or another, are involved in regulating renal transport of sodium, contributing to its retention in the body.

Our previous results[34] indicate a significantly greater accumulation of the G allele of the *ADD1*G460T SNP among patients with salt-resistant AH than among patients with SSH. Moreover, according to the literature data, TT and TG variants of the *ADD1* rs4961 (G460T) SNP predispose one to salt sensitivity, that is, the T allele of the *ADD1* rs4961 (G460T) SNP plays a role in forming salt sensitivity.

Hunt et al.[35] showed that in AH patients with the T allele of the *AGT* rs699 **(**M235T) SNP the decrease in BP with salt restriction in food was more pronounced than in the carriers of the M allele, which indicates the higher salt sensitivity of the those with the T allele.

An analysis of the literature data demonstrates the presence of genetic determinants in the development of SSH, ethnic differences in the prevalence and associative links of AH candidate genes with the development of the salt-sensitivity phenotype and, accordingly, the complicated course of AH. In addition, the role of epigenetic mechanisms

in the development of a complicated course of AH is not unimportant. However, as these data are scarce and somewhat contradictory, further extended searches in this direction are required, especially in the Aral Sea region.

Competing Interests

The authors declare that they have no competing interests.

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