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RESEARCH OF ASSOCIATION OF POLYMORPHIC VARIANTS OF GENES DOPAMINE SYSTEM'S (*DRD1, DRD2, DRD3, DRD4, TH, COMT* AND *MAO-B*) WITH IDIOPATHIC PARKINSON'S DISEASE

ABSTRACT

The dopamine metabolism disorder played a major role in the pathogenesis of Parkinson's disease (PD). We analyzed the polymorphic variants of the genes of the dopaminergic system: the *rs4532* of the *DRD1* gene, *Taq1* and *rs6275* of the *DRD2* gene, *rs6280* of the *DRD3* gene, *VNTR 120bp, VNTR 48bp* and *rs747302* of the *DRD4* gene (dopamine receptors), *(TCAT)n-repeats* of the *TH* gene (tyrosine hydroxylase), *rs4680* of the *COMT* gene (catechol-O-methyltransferase) and *rs1799836* of the *MAO-B* gene (monoamine oxidase B). The study included 264 patients with idiopathic PD and 314 healthy individuals of the Tatar ethnicity living on the territory of the Republic of Bashkortostan (RB). There is the association of the allele *rs4680*G* and the genotype *rs4680*G/G* of the *COMT* gene with PD development ($p=0,5*10^{-5}$; OR=1,73 and $p=0,36*10^{-4}$; OR=2,22, respectively), especially its akinetic-rigid-trembling form ($p=10^{-6}$; OR=2,86 and $p=0,3*10^{-5}$; OR=4,87, respectively) and its manifestation after 60 years ($p=0,12*10^{-3}$; OR=2,03 and $p=0,14*10^{-2}$; OR=2,51, respectively) in Tatar ethnicity. There is the association of allele *rs1799836*C* of the *MAO-B* gene with PD development in Tatar men ($p=0,7*10^{-3}$; OR=2,88). A complex analysis using the APSampler algorithm showed that the most significant combination associated with increased PD development was the combination of *rs4680(COMT)*G* and *(TCAT)nTH*8* alleles with *rs6311(HTR2A)*A* and *rs6296(HTR1B)*G* alleles of the genes of serotonine receptors which we investigated earlier. The only protective combination was triallelic combination of *rs4532(DRD1)**T, *rs4680(COMT)*A* and *rs1800532(TPH1)*T* alleles.

Keywords: Parkinson's disease, dopamine, polymorphic variants of the gene, dopamine receptors, monoamine oxidase B, tyrosine hydroxylase, catechol-O-methyltransferase.

INTRODUCTION

Congenital adrenal cortex dysfunction (ADHD, adrenogenital syndrome (AGS), congenital adrenal hyperplasia) is a group of diseases with an autosomal recessive type of inheritance, which is based on a defect of one of the enzymes or transport proteins that participate in the biosynthesis of cortisol in the adrenal cortex [2].

For the first time the disease was described by Phillips in 1886 as pseudohermaphroditism in a girl at the age of 19 days. In 1924 O.V. Vereshchinsky for the first time in the domestic literature cited information on 12 cases of adrenal-sexual syndrome. In the years 1950-1952. F.C.Bartter, F.Albright, A.Leaf, E. Dempsye, E. Carroll, L. Wilkins deciphered the essence of this disease, the biosynthesis of hydrocortisone. VDKN is the most common pathology of the adrenal glands in children (1 case per 5000 born).

Neonatal screening contributes to the early diagnosis of ACS, especially in boys before the development of clinical symptoms, to the early onset of substitution therapy and the safe social adaptation of children. Coverage of newborns with neonatal screening in the RS (Y) annually increases. With timely treatment of adrenogenital syndrome, the rates of physical development and puberty of the child are approaching the norm.

All patients have a lossy form of the disease. Analysis of patients identified by neonatal screening did not determine significant differences in gender, place of residence. In girls, the diagnosis was made immediately after birth due to the presence of virile syndrome. A case of an incorrect determination of the sex in a girl at birth was described on the patient's medical chart and was diagnosed with hypospadias. Substitution therapy for the majority was started up to 21 days. All patients receive replacement therapy with glucocorticoids and mineralocorticoids (Cortef, Cortineff) from the time of diagnosis in an individual dosage, depending on age. Acceleration of bone age is observed only in one child, in three, a decrease in the rate of growth and a lack of body weight.

MATERIALS AND METHODS

The order of the Ministry of Health of the Republic of Sakha (Yakutia) of March 20, 2006 was issued to organize screening, introduce new methods, organize diagnostic and therapeutic care. 01-8 / 4-134a "On the progress of the activities of the section of the national project" Health "on the examination of newborn children for hereditary diseases." The Order of the Republic of Belarus No. 1-NCM dated August 31, 2006. №01-0108 / 91 "About rendering medical aid to children with cystic fibrosis, adrenogenital syndrome, galactosemia, phenylketonuria and congenital hypothyroidism, revealed by neonatal screening" [5]. The screening procedure includes blood sampling in full-term newborns on day 4 of life, in preterm patients on day 7 and determination of 17-hydroxyprogesterone (17-ONP) levels in samples using special screening kits. The level of 17-SNP in blood samples is determined by the immunofluorescence method (test kits "Delfia 17-α-OH Progesteron», Finland, and «17-α-OH-Progesterone-Immunoskrin», Russia). The following provisions are taken into account when interpreting the indicators of 17-SNP: - the level of 17-SNP for full-term children (the gestation period is more than 37 weeks, the body weight is more than 2000 gr.) Normally up

to 30 nmol / l; At a level of 17-SNP 30-90 nmol / l - the result is regarded as questionable (false positive), re-determination of 17-SNP in the control spot is required; At a level of 17-SNP more than 90 nmol / l - the result is positive, the information is transmitted at the location of the child. For preterm infants (gestation period 33-36 weeks, body weight less than 2000 g.), The normative index of 17-OHP is up to 60 nmol / l. In cases where the premature baby has levels in 17-SNP within 60-100 nmol / L - the result is doubtful (false positive). In premature infants with a level of 17-SNP more than 100 nmol / L, the result is positive, information is given at the location of the child. In children with deep prematurity (gestation period of 23-32 weeks), the result should be considered positive at a level of 17-SNP above 150 nmol / l. In this case, it is necessary to send information to the hospital or to the children's polyclinic where the child is, and to re-take and screen-test the blood sample [4].

Data on neonatal screening for the period 2006-2016. Provided by the laboratory of the Medical Genetic Center (MHC) of the Perinatal Center, data on patients - the endocrinological department of the Pediatric Center of the State Bank of the Republic of Sakha (Yakutia) «Republican Hospital No. 1-National Center of Medicine». A retrospective study of stationary charts of children with a diagnosis of congenital adrenal cortex dysfunction was carried out. Data on patients are taken from the register of admission of patients with endocrinology department (form 001 / y).

RESULTS

According to the neonatal screening program in RS (Y), only 160 626 newborns were examined, the diagnosis of VDKN was established in 11 children, the coverage was 99.5%. The frequency of VDKN 1:14 is 602 newborns. In 2006, out of 5559 newborns that had undergone the study, no ACS was detected. In 2012 Of the 16832 newborns studied, the detectability of ACS was the highest and amounted to 4 people per year at a frequency of 1: 4208 newborns (Table 1). Thus, the prevalence of ACS in the Republic of Sakha (Yakutia) is 1 case at 14,602 (Figure 1), lower than in the Russian Federation 1: 7650 and its regions: in the Ural Federal District 1: 5781, in the Siberian Federal District 1: 9681. The most frequent occurrence of ACS is observed in Alaska residents 1: 280 newborns, the lowest in China 1:28 000 [3].

Analysis of patients identified by neonatal screening did not determine significant differences in gender - 5 boys (45%), 6 (55%) girls, sex ratio 1: 1.5, place of residence - urban 5 (45%), rural 6 (55%), nationality - 4 (36%) of the Yakut child, 5 (46%) Russians, and 2 (18%) other nationalities.

Table 1

The distribution of the frequencies of alleles and genotypes of the polymorphic loci of the genes of the dopaminergic system in patients with Parkinson's disease and in the control group

The groups	Frequencies of alleles, n (p, %)		Frequencies of genotypes, n (p, %)			N
	*C	*T	*C/C	*C/T	*T/T	
1	2	3	4	5	6	7
***DRD1* (rs4532)**						
The control group	192 (28,15)	490 (71,85)	26 (7,62)	140 (41,06)	175 (51,32)	341
Patients with Parkinson's disease	120 (27,27)	320 (72,73)	19 (8,64)	82 (37,27)	119 (54,09)	220
RT form	47 (27,98)	121 (72,02)	10 (11,9)	27 (32,14)	47 (55,95)	84
AR form	19 (31,67)	41 (68,33)	4 (13,33)	11 (36,67)	15 (50)	30
ART form	26 (26)	74 (74)	2 (4)	22 (44)	26 (52)	50
Manifestation of up to 45 years	10 (26,32)	28 (73,68)	2 (10,53)	6 (31,58)	11 (57,89)	19
Manifestation 45-60 years	34 (27,42)	90 (72,58)	6 (9,68)	22 (35,48)	34 (54,84)	62
Manifestation after 60 years	53 (26,77)	145 (73,23)	8 (8,08)	37 (37,37)	54 (54,55)	99
***DRD2* (Taq1, или 32806C>T)**						
	*A1	*A2	*A1/A1	*A1/A2	*A2/A2	
The control group	176 (22,56)	604 (77,44)	17 (4,36)	142 (36,41)	231 (59,23)	390
Patients with Parkinson's disease	107 (24,21)	335 (75,79)	14 (6,33)	79 (35,75)	128 (57,92)	221
RT form	28 (19,44)	116 (80,56)	5 (6,94)	18 (25)	49 (68,06)	72
AR form	16 (25)	48 (75)	1 (3,12)	14 (43,75)	17 (53,12)	32
ART form	32 (25,4)	94 (74,6)	4 (6,35)	24 (38,1)	35 (55,56)	63
Manifestation of up to 45 years	8 (19,05)	34 (80,95)	2 (9,52)	4 (19,05)	15 (71,43)	21
Manifestation 45-60 years	30 (24,19)	94 (75,81)	3 (4,84)	24 (38,71)	35 (56,45)	62
Manifestation after 60 years	48 (23,76)	154 (76,24)	6 (5,94)	36 (35,64)	59 (58,42)	101
***DRD2* (rs6275 или NcoI)**						
	*A	*G	*A/A	*A/G	*G/G	
The control group	331 (39,4)	509 (60,6)	70 (16,67)	191 (45,48)	159 (37,86)	420
Patients with Parkinson's disease	214 (41,47)	302 (58,53)	46 (17,83)	122 (47,29)	90 (34,88)	258
RT form	76 (41,3)	108 (58,7)	19 (20,65)	38 (41,3)	35 (38,04)	92
AR form	32 (47,06)	36 (52,94)	7 (20,59)	18 (52,94)	9 (26,47)	34
ART form	52 (39,39)	80 (60,61)	10 (15,15)	32 (48,48)	24 (36,36)	66
Manifestation of up to 45 years	15 (32,61)	31 (67,39)	3 (13,04)	9 (39,13)	11 (47,83)	23
Manifestation 45-60 years	61 (42,96)	81 (57,04)	15 (21,13)	31 (43,66)	25 (35,21)	71
Manifestation after 60 years	99 (42,67)	133 (57,33)	20 (17,24)	59 (50,86)	37 (31,9)	116
***DRD3* (rs6280 или Ser9Gly)**						
	*C	*T	*C/C	*C/T	*T/T	
The control group	179 (25,07)	535 (74,93)	27 (7,56)	125 (35,01)	205 (57,42)	357
Patients with Parkinson's disease	120 (24,39)	372 (75,61)	16 (6,51)	88 (35,77)	142 (57,72)	246
RT form	44 (23,66)	142 (76,34)	6 (6,45)	32 (34,41)	55 (59,14)	93
AR form	15 (24,19)	47 (75,81)	2 (6,45)	11 (35,48)	18 (58,06)	31
ART form	31 (26,27)	87 (73,73)	4 (6,78)	23 (38,98)	32 (54,24)	59
Manifestation of up to 45 years	9 (22,5)	31 (77,5)	2 (10)	5 (25)	13 (65)	20
Manifestation 45-60 years	33 (23,57)	107 (76,43)	2 (2,86)	29 (41,43)	39 (55,71)	70
Manifestation after 60 years	54 (24,11)	170 (75,89)	8 (7,14)	38 (33,93)	66 (58,93)	112
***DRD4* (VNTR 120bp)**						
	*S	*L	*S/S	*S/L	*L/L	
The control group	124 (15,9)	656 (84,1)	8 (2,05)	108 (27,69)	274 (70,26)	390
Patients with Parkinson's disease	68 (15,39)	374 (84,61)	9 (4,07)	50 (22,62)	162 (73,31)	221
RT form	20 (14,09)	122 (85,91)	3 (4,23)	14 (19,72)	54 (76,06)	71
AR form	7 (10,94)	57 (89,06)	0 (0)	7 (21,88)	25 (78,12)	32
ART form	22 (17,19)	106 (82,81)	4 (6,25)	14 (21,88)	46 (71,88)	64
Manifestation of up to 45 years	8 (19,05)	34 (80,95)	2 (9,52)	4 (19,05)	15 (71,43)	21
Manifestation 45-60 years	16 (12,90)	108 (87,10)	1 (1,61)	14 (22,58)	47 (75,81)	62
Manifestation after 60 years	30 (14,85)	172 (85,15)	5 (4,95)	20 (19,80)	76 (75,25)	101
***DRD4* (rs747302 или 616C>T)**						
	*C	*G	*C/C	*C/G	*G/G	
The control group	285 (37,4)	477 (62,6)	48 (12,6)	189 (49,61)	144 (37,8)	381
Patients with Parkinson's disease	168 (37)	286 (63)	30 (13,22)	108 (47,58)	89 (39,21)	227
RT form	59 (37,82)	97 (62,18)	12 (15,38)	35 (44,87)	31 (39,74)	78
AR form	23 (38,33)	37 (61,67)	5 (16,67)	13 (43,33)	12 (40)	30

End of table 1

1	2	3	4	5	6	7
AR form	44 (36,07)	78 (63,93)	6 (9,84)	32 (52,46)	23 (37,7)	61
ART form	12 (31,58)	26 (68,42)	1 (5,26)	10 (52,63)	8 (42,11)	19
Manifestation 45-60 years	53 (40,15)	79 (59,85)	11 (16,67)	31 (46,97)	24 (36,36)	66
Manifestation after 60 years	66 (33,33)	132 (66,67)	11 (11,11)	44 (44,44)	44 (44,44)	99
***MAO-B* (rs1799836) (men)**						
	*C	*T	*C/C	*C/T	*T/T	N
The control group	74 (29,13)	180 (70,87)	37 (29,13)	0	90 (70,87)	127
Patients with Parkinson's disease	76 (35,19)	140 (64,81)	38 (35,19)	0	70 (64,81)	108
RT form	24 (27,91)	62 (72,09)	12 (27,91)	0	31 (72,09)	43
AR form	10 (35,71)	18 (64,29)	5 (35,71)	0	9 (64,29)	14
ART form	26 (54,17)	22 (45,83)	13 (54,17)	0	11 (45,83)	24
Manifestation of up to 45 years	6 (33,33)	12 (66,67)	3 (33,33)	0	6 (66,67)	9
Manifestation 45-60 years	16 (40)	24 (60)	8 (40)	0	12 (60)	20
Manifestation after 60 years	38 (34,55)	72 (65,45)	19 (34,55)	0	36 (65,45)	55
***MAO-B* (rs1799836) (women)**						
The control group	171 (36,69)	295 (63,31)	33 (14,16)	105 (45,06)	95 (40,77)	233
Patients with Parkinson's disease	96 (35,56)	174 (64,44)	21 (15,56)	54 (40)	60 (44,44)	135
RT form	28 (27,45)	74 (72,55)	5 (9,8)	18 (35,29)	28 (54,91)	51
AR form	16 (50)	16 (50)	4 (25)	8 (50)	4 (25)	16
ART form	21 (30,88)	47 (69,12)	5 (14,71)	11 (32,35)	18 (52,94)	34
Manifestation of up to 45 years	7 (31,82)	15 (68,18)	1 (9,1)	5 (45,45)	5 (45,45)	11
Manifestation 45-60 years	31 (32,98)	67 (67,02)	5 (10,2)	21 (42,86)	23 (46,94)	49
Manifestation after 60 years	41 (36,61)	71 (63,39)	11 (19,64)	19 (33,93)	26 (46,43)	56
***COMT* (rs4680 или 1947G>A)**						
	*H (G)	*L (A)	*H/*H (G/G)	*L/*H (G/A)	*L/*L (A/A)	N
The control group	306 (48,73)	322 (51,27)	67 (21,34)	172 (54,78)	75 (23,89)	314
Patients with Parkinson's disease	328 (62,12)	200 (37,88)	100 (37,8)	128 (48,48)	36 (13,64)	264
RT form	100 (56,82)	76 (43,18)	30 (34,09)	40 (45,45)	18 (20,45)	88
AR form	40 (58,82)	28 (41,18)	11 (32,35)	18 (52,94)	5 (14,71)	34
ART form	95 (73,08)	35 (26,92)	37 (56,92)	21 (32,31)	7 (10,77)	65
Manifestation of up to 45 years	17 (50)	17 (50)	5 (29,41)	7 (41,18)	5 (29,41)	17
Manifestation 45-60 years	56 (50,91)	54 (49,09)	16 (29,10)	24 (43,64)	15 (27,27)	55
Manifestation after 60 years	104 (65,82)	54 (34,18)	32 (40,51)	40 (50,63)	7 (8,86)	79

Note: n - number of the chromosomes, p – the frequency (%), N - number of individuals; RT - the rigidly-trembling form; AR – the akinetic-rigid form; ART – the akinetic-rigid-trembling form.

For 10 years 376 (0.23%) children had an elevated level of 17-ONP. Retest was performed in 214 children with elevated levels of 17-SNP, among them term infants 101 (47%), premature infants 113 (53%) (Table 2). As a result of the retest, an increased level of 17-SNP in 56 children, among them preterm infants 43 (77%), full-term children - 13 (23%). ACS was established in 11 children, respectively 45 children had a transient increase in 17-ONP. The level of increase in 17-SNP in these cases at birth varied from 65 to 1158 nmol / l. Concentrations of 17-hydroxyprogesterone may be elevated, even when there is no deficiency of this enzyme. This is due to the peculiarities of adrenal steroidogenesis, the immaturity of the axis "hypothalamus - pituitary - adrenal glands". It happens in preterm; Children with birth trauma or severe physical illness; Against intravenous infusion; In newborns with high blood bilirubin levels; At birth with low body weight at normal gestation terms. False negative results can also be determined if the mother during the pregnancy took dexamethasone for the prevention (therapy) of lung fetal diseases or so treated a newborn (with a lack of surfactant). In such cases it is recommended to check the hormone index repeatedly - after 5-7 days [4].

The condition of children with ACS at birth in 9 children was noted as satisfactory, 2 children needed resuscitation. On the Apgar scale, almost all have high scores. The physical parameters of newborns correspond to normal indices.

The level of 17-SNP for neonatal screening in the identified patients averaged 235.26 ± 1.09 nmol / l, (the range of oscillations from 67.17 ± 1.09 nmol / l to 413.34 ± 1.09 nmol / l). All patients have a lossy form of the disease. The diagnosis of VDKN in 3 boys was put on the 21st day and the 1st month of life against the background of a saltwort crisis, in 2 boys, VDKN was detected for neonatal screening. In 4 girls, the diagnosis was made immediately after birth by the presence of a viril syndrome and the degree of virilization according to the Prader scale was II-III. In 1 girl with virilization of external genital organs of III-IV degree, sex at birth was incorrectly determined and with the diagnosis: hypospadias entered the II stage of treatment of the Perinatal Center. In 1 female, the ACS was confirmed at 5 months of age, during the examination in the psycho-neurological department No. 2, due to the irregular structure of the external genitalia (Fig. 2).

The purpose of substitution treatment for children with VDKN is not to simulate physiological secretion, but to restore the deficit of corticosteroids, the secretion of which is reduced as a result of an enzymatic defect with suppression of increased secretion of corticotropin releasing hormone and ACTH, in preventing virilization, optimizing patient growth, ensuring normal sexual Maturation and potential fertility [1].

All patients receive replacement therapy with glucocorticoids and mineralocorticoids (Cortef, Cortineff) from the moment of diagnosis in the individual dosage depending on the age (Fig. 3). Acceleration of bone age is observed only in 1 (9%) of the child, at the age of 8 years the bone age corresponds to 11-12 years. This child needs to reduce the dose of substitution therapy. In 3 (27%) children there is a decrease in the rate of growth and a lack of body weight. In this group of children, an increase in the dose of hormonal drugs is required. The remaining 5 (45%) children have a normal growth rate and bone maturation. That indicates adequate therapy.

CONCLUSION

1. Neonatal screening coverage from 40.8% in the first years of its introduction increased to 99.8% in the period from 2006 to 2016. The frequency of ACS was 1:14 602, which shows a low incidence rate in comparison with other regions of the Russian Federation.

2. Analysis of the anamnesis, distribution by place of residence, by gender, by nationality, by the state of health at birth, by physical parameters, the Apgar score did not reveal any specific features. In all cases, there is a salt-losing form of the disease. In girls, the diagnosis of ACS is assumed at birth, due to the virilization of NGOs, in men, the diagnosis was made on the basis of clinical symptoms and neonatal screening. In most cases, the clinic begins on the 21st day of life, i.e. it is necessary for doctors neonatologists and pediatricians to send timely to the retest of newborns with increased results, to be wary of ACS, to carefully inspect the external genitalia. The average level of 17-SNP for neonatal screening was 235.26 ± 1.09 nmol / l.

3. Properly selected and timely therapy of GCS and ISS provides normal growth rates, bone maturation, sexual develop-

Table 2

Frequency distribution of alleles and genotypes of the polymorphic loci of the genes of the dopaminergic system in patients with Parkinson's disease and in the control group

Alleles	Comparable groups		Parkinson's		Genotypes	Control		Parkinson's	
	n	p (%)	n	p (%)		n	p (%)	n	p (%)
***DRD4* (VNTR 48bp)**									
*2R	78	10,29	33	7,21	*2R/2R	17	4,49	7	3,06
					*2R/3R	3	0,79	3	1,31
					*2R/4R	41	10,82	15	6,55
*3R	29	1,19	17	3,71	*2R/5R	0	0	1	0,44
					*2R/7R	0	0	0	0
					*2R/8R	0	0	0	0
*4R	605	79,82	367	80,13	*3R/3R	4	1,06	2	0,87
					*3R/4R	16	4,22	10	4,37
					*4R/4R	261	68,87	159	69,43
*5R	21	2,77	17	3,71	*4R/5R	9	2,38	8	3,49
					*4R/7R	16	4,22	13	5,68
					*4R/8R	1	0,26	1	0,44
*7R	24	3,17	19	4,15	*5R/5R	5	1,32	3	5,68
					*5R/7R	1	0,26	1	0,44
					*7R/7R	3	0,79	2	0,88
*8R	1	0,13	3	0,66	*8R/8R	8	2,11	1	0,44
					N	379		229	
TH (repeats (TCAT)n)									
*6	159	26,68	109	25,95	*6/6	18	6,04	14	6,67
					*6/7	33	11,07	27	12,86
					*6/8	19	6,38	16	7,62
*7	99	16,61	86	20,48	*6/9	24	8,05	13	6,19
					*6/9,3	46	15,44	24	11,43
					*6/10	1	0,34	1	0,48
*8	66	11,07	48	11,43	*7/7	2	0,68	6	2,86
					*7/8	11	3,69	4	1,91
					*7/9	17	5,71	15	7,14
*9	101	16,95	71	16,91	*7/9,3	33	11,07	28	13,33
					*7/10	1	0,34	0	0
					*8/8	1	0,34	1	0,48
*9,3	165	27,69	105	25	*8/9	13	4,36	15	7,14
					*8/9,3	20	6,71	11	5,24
					*8/11	1	0,34	0	0
*10	22	3,69	16	3,81	*9/9	10	3,41	4	1,91
					*9/9,3	26	8,73	20	9,52
					*9,3/9,3	20	6,71	11	5,24
*11	2	0,34	0	0	*10/10	1	0,34	0	0
					N	298		210	

Table 3

Comparative analysis of the frequencies of alleles and genotypes of the polymorphic loci of the genes of the dopaminergic system with the development of Parkinson's disease, its clinical forms and age of manifestation

Genotipe, allele	Comparable groups	p	χ^2	OR	95% CI
***MAO-B* (rs1799836) (мужчины)**					
*C/*C	ART form / control group	0,0169* (0,051**)	5,71	2,58	1,18-6,70
*T/*T		0,0169* (0,051**)	5,71	2,58	1,18-6,70
*C		0,0007*	11,42	2,88	1,53-5,39
*T		0,0007*	11,42	0,35	0,19-0,65
***COMT* (rs4680 или 1947G>A)**					
*H/*H (G/G)	patients with Parkinson's disease / control group	0,000012* (0,000036**)	19,10	2,22	1,56-3,25
*L/*H (G/A)		0,13	2,28	0,78	0,56-1,08
*L/*L (A/A)		0,0018* (0,0054**)	9,71	0,50	0,33-0,78
*H (G)		0,000005*	20,78	1,73	1,36-2,18
*H/*H (G/G)	ART form / control group	0,000001* (0,000003**)	34,25	4,87	2,78-8,53
*L/*H (G/A)		0,00097* (0,0029**)	10,88	0,34	0,22-0,69
*L/*L (A/A)		0,02* (0,06**)	5,46	0,39	0,17-0,88
*H (G)		0,000001*	25,63	2,86	1,88-4,34
*H/*H (G/G)	manifestation after 60 years / control group	0,00045* (0,00135**)	12,31	2,51	1,49-4,24
*L/*H (G/A)		0,51	0,44	0,85	0,52-1,39
*L/*L (A/A)		0,000001* (0,000003**)	53,66	0,08	0,04-0,18
*H (G)		0,00012*	14,79	2,03	1,41-2,92

Note: $\chi 2$ - the criterion of independence; OR - odds ratio; 95% CI - 95% confidence interval; p – the significance level; * - the value of p <0.005; ** - the significance level p with Bonferroni amendment.

ment and normal reproductive function.

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INVESTIGATION OF THE ROLE OF CYTOKINE GENES POLYMORPHISMS IN THE DEVELOPMENT OF THE URTICARIA IN THE REPUBLIC OF BASHKORTOSTAN

ABSTRACT

At present, there is a steady increase in the incidence and prevalence of allergic skin diseases in the world, affecting up to 25% of the population in different countries. Urticaria is an etiologically heterogeneous group of diseases and conditions characterized by the formation of itching rashes on the skin. According to epidemiological studies, at least once during a lifetime this pathology is observed in 15-25% of the population. Urticaria is a polyethological disease. Allergic mechanisms of tissue damage are involved in the development of the allergic form of hives. Cytokines play a key role in all stages of development and maintenance of allergic inflammation. The purpose of this study was to investigate the polymorphic loci of interleukins genes IL4 (rs2243250), IL4R (rs1805010), IL10 (rs1800872), IL13 (rs20541) and tumor necrosis factor gene TNF (rs1800629) in patients with hives and in the control group of individuals. The material for the study was DNA samples of 102 unrelated individuals with urticaria, and 153 healthy individuals living in the Republic of Bashkortostan. The DNA was isolated by phenol-chloroform extraction. Genotyping of polymorphic loci was carried out by real-time PCR. As a result of the analysis, we showed that the rs1800629*G allele and the rs1800629*G/G genotype of the TNF gene polymorphism are the markers of an increased risk of developing of chronic urticaria, rs2243250*C allele of the IL4 gene – of the acute urticaria, and the rs1800629*G/A genotype of the TNF gene is a marker of the urticaria with concomitant allergic diseases development. The data obtained by us are in part consistent with the results of other authors. Thus, in patients from Japan and Canada, the SNP rs2243250 of the IL4 gene is associated with the development of atopic dermatitis. The association of the TNF gene rs1800629 polymorphism with the development of bronchial asthma and atopy is indicated in patients from the USA and Spain. As in our study, patients with allergic dermatoses from Japan did not have an association of the IL4R gene SNP rs1805010 with the development of the disease. Nevertheless, a number of other studies have shown the association with the development of various allergic diseases of all the polymorphic loci we studied. Thus, this study shows an association with the development of urticaria of polymorphic variants of the TNF and IL4 genes.

Keywords: urticaria, association analysis, cytokines, genes, polymorphic variants.