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Research Article

Results Frequency Analysis Distribution of Alleles and Genotypes of the Polymorphic Marker Rs1800471 of the Tgfb1 Gene in Patients with Ronchopathy

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Abstract

Introduction: Snoring is the most common type of sleep apnea. Ronchopathy is caused by obstruction of the upper airways. This condition is characterized by repeated pauses in breathing during sleep, despite the efforts of the respiratory muscles, and, as a rule, is associated with a decrease in blood oxygen saturation.

The Research Objective: To study the distribution of genotypic forms of the TGFb1 gene locus and evaluate their role in the development and clinical course of ronchopathy.

Materials and Methods: 208 patients with various diseases of the upper respiratory tract, with nasal breathing disorders, causing ronchopathy, who were hospitalized in the ENT department of the multidisciplinary clinic of the Tashkent Medical Academy for 2015 to 2021, were examined. The control group consisted of 50 apparently healthy people who agreed to participate in the study (students, masters, clinical residents). Among the sick men there were 144 (73%), women - 64 (27%).

Results and Discussion: For an unambiguous assessment of the role of the rs1800471 polymorphism of the TGFb1 gene in the formation of impaired nasal breathing and the development of ronchopathy, we believe that additional and in-depth studies are necessary with an increase in the number of patients and control. It is interesting to note that the adverse effect of this genotype was observed exclusively in patients with ronchopathy, while in patients with ronchopathy, the frequency of this genotype did not differ in comparison with the control group, i.e. there is a significant tendency to an increase in the genotype with an increase in the severity of the pathology.

Conclusion: Since this work is one of the few works on the study of the relationship between rs1800471 of the TGFb1 gene and the risk of developing ronchopathy, our data may become the subject of further discussions.

Keywords: Ronchopathy; Gene; Allele; Genotype; Polymorphism; Sleep Apnea

Introduction

Snoring is the most common type of sleep apnea. Ronchopathy is caused by obstruction of the upper airways. This condition is characterized by repeated pauses in breathing during sleep, despite the efforts of the respiratory muscles, and as a rule, is associated with a decrease in blood oxygen saturation [1]. The review pres-

ents literature data on the intermediate phenotypes of Ronchopathy, in the development of which a genetic component is likely to take place. It is indicated that the study of the genetic basis of various phenotypes of ronchopathy will help to better understand the contribution of genetic factors to the development of the disease. The genes responsible for the predisposition to the development of four main phenotypes of ronchopathy have been described. Two main approaches to carrying out molecular genetic research in ronchopathy are characterized: analysis of genetic associations and linkadic analysis. Given the widespread prevalence and social significance of ronchopathy, it is necessary to carry out its timely prevention and diagnosis. Adequate treatment of ronchopathy and its consequences can not only reduce the risk of fatal complications of the disease, but also completely eliminate its symptoms [2,3].

There is growing evidence that genetic factors are involved in the development of ronchopathy. In some cases, this pathological condition is clearly genetically determined. The interaction of genes that affect obesity, craniofacial morphology, the occurrence of respiratory disorders, daytime sleepiness, with "favorable" external factors, can lead to the formation of a predisposition to ronchopathy, and therefore ronchopathy should be considered as a multifactorial (polygenic) hereditary disease. In general, about 35 - 40% of all cases of ronchopathy can be explained by genetic factors [4]. Thus, a number of researchers believe that in the presence of relatives of the first degree of kinship in the family, suffering from ronchopathy, the risk of developing this disease in a proband increases more than 2 times compared with the average population [5]. Knowing the contribution of genetic factors to the development of ronchopathy, it is easier to understand the pathogenesis of this complex disease, which can be an independent nosology or part of a larger syndrome associated with respiratory, cardiovascular or endocrine dysfunction. Identification of genetic variants that can increase the risk of ronchopathy should lead to a decrease in the incidence, timely diagnosis and treatment of this syndrome in the early stages of development. An increase in the genetic risk of ronchopathy can occur along at least four intermediate pathways of pathogenesis: 1) obesity and metabolic syndrome [6]; 2) craniofacial morphology [7]; 3) ventilation control and the occurrence of respiratory disorders [8]; 4) control of sleep and circadian rhythms sleep - wakefulness [9]. The identification of genes that determine these four main intermediate phenotypes is very important, since these same genes can be decisive in the formation of ronchopathy (See table 1.2) [10-13]. For example, the main reasons for the formation of ronchopathy in children are adenotonsillar hypertrophy, maxillofacial dysmorphia and obesity. Allergic rhinitis plays an important role in children and adults, which is considered as an independent risk factor for ronchopathy in children [14-16].

There are two main approaches to conducting molecular genetic research in ronchopathy: analysis of genetic associations and linkade analysis. Analysis of genetic associations (study of single nucleotide polymorphisms - SNPs) in candidate genes is the leading approach in studying the role of the genetic component in the pathogenesis of multifactorial human diseases, in which the cumulative action of a complex of genes that determine the nature of key biochemical and immunological processes in the body plays an important role in hereditary predisposition. (features of metabolism, the nature of the immune response, the efficiency of energy reactions, etc.). Isolation of the most significant candidate genes influencing the likelihood of ronchopathy development from the general "genetic background" is the essence of the analysis of associations [17-20].

Studies of this type usually compare the genomes of a group of people with ronchopathy with those of a control group, which includes healthy volunteers of comparable age, sex, and other characteristics. The research material is DNA samples from each participant. The identified variants of genomes (more precisely, a set of alleles), which are significantly more common in patients with ronchopathy, are referred to as associated with the disease.

Materials and Methods

To solve the set tasks, 208 patients with various diseases of the upper respiratory tract, with nasal breathing disorders, causing ronchopathy, who were hospitalized in the ENT department of the multidisciplinary clinic of the Tashkent Medical Academy for 2015 to 2021, were examined. The control group consisted of 50 apparently healthy people who agreed to participate in the study (students, masters, clinical residents). Among the sick men there were 144 (73%), women - 64 (27%). The age of the patients ranged from 18 to 70 years, averaging 44.5 ± 6.8 years.

Molecular genetic studies were carried out in the Department of Molecular Medicine and Cell Technologies of the RSNPMC Hematology.

This part of the work consisted of several stages:

- Blood sampling.
- Isolation of DNA from peripheral blood lymphocytes.
- Carrying out PCR.
- Conducting electrophoresis and visualizing the results (if necessary).

The analysis of the TGFb1 gene polymorphism associations was carried out using a case-control model (case-control, comparison of two samples). The sample "case" was formed from 104 patients with ronchopathy.

Genomic DNA preparations, both isolated independently and stored in the DNA bank of the RSNPMC Hematology of the Ministry of Health of the Republic of Uzbekistan, were used as material for the control sample. The control group consisted of 50 healthy unrelated donors (Uzbek nationality), matched by sex and age to the examined group of patients ($p > 0.05$), and had no history of ronchopathy pathology.

Genetic research and analysis of the data obtained was carried out in accordance with the principles of GRIPS in order to increase the transparency and quality of risk prediction [10].

The AmpliPrime RIBO-prep reagent kit (AmpliSens, Russia) was used to isolate DNA from peripheral blood. The isolated DNA concentrations were measured on a NanoDrop 2000 spectrophotometer (NanoDrop Technologies, USA) at a wavelength of A260/280 nm. The purity of all samples of the isolated DNA preparation, determined by the ratio A260/280, was 1.7/1.8. PCR analysis was performed using Applied Biosystems 2720 (USA) and CG1-96 (Corbett Research, QUAGEN, Germany) thermal cyclers. The following reagents and enzymes were used in the work: acrylamide, bis-acrylamide, EDTA, 5% glycerol solution, proteinase K (Sigma, USA), TEMED, sodium dodecyl sulfate, Tris-HCL (Serva, Germany), 2 -mercaptoethanol ("Ferax", Germany), deoxynucleotide triphosphates, dideoxynucleotide triphosphates, Triton X100, magnesium chloride, sodium chloride, ammonium sulfate, ammonium persulfate, thermostable DNA polymerase Thermus aquaticus (NPO "Biomereotide", Novosibirsk), test systems by OOO NPF Litekh (Moscow) and OOO InterLabService (Moscow). For molecular genetic studies, the following equipment was used: Applied Biosystems 2720 (USA) and CG1-96 thermal cyclers (Corbett Research, QUAGEN Germany), and RotorGeneQ (QUAGEN Germany), laminar box (Germany), centrifuges (Eppendorf, Hittich, Germany), vortex (Eppendorf, Germany), thermostats, spectrophotometer NanoDrop 2000 "Thermo Scientific" (USA), device for horizontal electrophoresis, power source (DNA-Technology, Russia), UV transilluminator with built-in digital camera, automatic pipettes (Sartorius, Finland) and etc.

Results and Discussion

Table 1 and 2 show the theoretical and actual (Hexp and Hobs, respectively) frequencies of alleles and genotypes in the samples of patients with ronchopathy and control. The frequency of occurrence of Arg and Pro alleles in the studied groups of patients and controls was 0.72/0.28 and 0.79/0.21, respectively.

Analysis of the distribution of rs1800471 genotypic variants of the TGFb1 gene showed that for this polymorphism the actual distribution of genotypes in the groups of patients with ronchopathy and control corresponds to the theoretically expected one at Hardy-Weinberg equilibrium ($p < 0.05$).

As can be seen from table 1, in the group of patients, the observed distribution of the homozygous Arg/Arg genotype is insignificantly higher than the theoretical one (0.54 versus 0.51, respectively; $\chi^2 = 0.13$; $p = 0.2$). On the contrary, the observed frequency of the heterozygous Arg/Pro genotype is statistically insignificantly higher than the expected one (0.36 versus 0.41, respectively; $\chi^2 = 0.66$; $p = 0.2$). The relative deviation of Hobs and Hexp turned out to be negative and amounted to: D = -0.12 (Table 2 and 3).

Main group					
Alleles	Allele frequency				
Arg	0,72				
Pro	0,28				
Genotypes	**Genotype frequency**		**Xi²**	**p**	**df**
	Observable	**Expected**			
Arg /Arg	0,54	0,51	0,13		
Arg / Pro	0,36	0,41	0,66		
Pro/ Pro	0,11	0,08	0,83		
Total	1.0	1.0	1,61	0,195	1

Table 1: Expected and observed frequencies of distribution of genotypes of a locus by RHW.

Control group					
Alleles	Allele frequency				
Arg	0,79				
Pro	0,21				
Genotypes	Genotype frequency		Xi^2	p	df
	Observable	Expected			
Arg /Arg	0,63	0,62	0,03		
Arg / Pro	0,31	0,34	0,24		
Pro/ Pro	0,06	0,05	0,44		
Total	1	1	0,71	0,378	1

Table 2: Expected and observed frequencies of distribution of genotypes of a locus by PXB.

Groups	No	Ne	D*
Main group	0,36	0,41	-0,12
Control group	0,31	0,34	-0,08
Note: D = (No - Ne)/Ne			

Table 3

In the control sample, the indicators of the observed and expected frequency of the homozygous genotype Arg/Arg corresponded to Hobs = 0.63 and Hexp = 0.62 (χ^2 = 0.03 and p = 0.4), the heterozygous genotype Arg/Pro-Hobs = 0.31 versus Hexp = 0.34 (χ^2 = 0.24 and p = 0.4). The relative deviation of Hobs and Hexp in this group also turned out to be negative D = -0.08 (Table 2 and 3).

The associative analysis of the rs1800471 locus of the TGFb1 gene in the studied groups of patients with ronchopathy and control was also carried out using the case-control design. The obtained results of the detection of this are presented in table 4 and 5 and indicate the presence of a tendency towards the contribution of the unfavorable Pro allele and the associated homozygous Pro/ Pro genotype in the development of ronchopathy.

As can be seen from table 4 and 5, in the studied groups of patients and controls, the proportion of Arg and Pro alleles was 71.6%/28.4% versus 78.7%/21.3%, respectively. Statistical processing, despite insignificant differences, revealed a noticeable tendency to an increase in the frequency of the unfavorable Pro al-

Num	Group	Allele frequency				Genotype distribution frequency					
		Arg		Pro		Arg /Arg		Arg / Pro		Pro/ Pro	
		n	%	n	%	n	%	n	%	n	%
1	Main group (n = 104)	149	71,63	59	28,37	56	53,85	37	35,58	11	10,58
	Mild ronchopathy (n = 67)	96	71,64	38	28,36	36	53,73	24	35,82	7	10,45
	Moderate ronchopathy (n = 37)	53	71,62	21	28,38	20	54,05	13	35,14	4	10,81
4	Control group (n = 101)	159	78,71	43	21,29	64	63,37	31	30,69	6	5,94

Table 4: Frequency of distribution of alleles and genotypes of Arg25Pro polymorphism in the TGFb1 gene in patient and control groups.

Alleles and genotypes	Number of examined alleles and genotypes				Xi2	p	RR	-95%CI	+ 95%CI	OR	-95%CI	+95%CI
	Main group		Control group									
	n	%	n	%								
Arg	149	71,6	159	78,71	2,75	0,58	0,91	0,61	1,35	0,68	0,44	1,07
Pro	59	28,4	43	21,29	2,75	0,42	1,10	0,67	1,80	1,46	0,93	2,30
Arg /Arg	56	53,85	64	63,37	1,91	0,56	0,85	0,50	1,44	0,67	0,39	1,18
Arg / Pro	37	35,58	31	30,69	0,55	0,49	1,16	0,67	1,99	1,25	0,70	2,23
Pro/ Pro	11	10,58	6	5,94	1,45	0,49	1,8	0,85	3,75	1,9	0,67	5,21

Table 5

lele and a decrease in the dominant wild allele Arg in patients with ronchopathy compared to conventionally healthy donors. The calculated odds ratio showed that the chance of detecting a functional unfavorable allele Pro in respondents with ronchopathy increased 1.5 times compared to representatives of the control group (χ^2 = 2.7; P = 0.4). The calculated relative risk of developing pathology was 1.46 with a confidence interval of 95% CI: 0.93 - 2.3.

The frequencies of Arg/Arg, Arg/Pro and Pro/Pro genotypes rs1800471 of the TGFb1 gene in the studied groups of patients with ronchopathy and control were: 53.8%,.35.6% and 10.6% versus 63.4%, 30.7% and 5.9%, respectively.

As can be seen, the frequency of the wild genotype G/G among patients with ronchopathy was lower than in the control group (79.6% versus 88.5%, respectively, with χ^2 = 2.8; P = 0.09; OR = 0.5; 95% CI0.2253-1.128).

There was no significant difference in the frequency of the heterozygous Arg/Pro genotype among patients compared to the control group (35.6% versus 30.7%, respectively). According to the odds ratio, the risk of developing impaired nasal breathing in patients with ronchopathy in the presence of this genotype does not increase significantly by 1.2 times (χ^2 = 0.5;P = 0.5; OR = 1.2; 95% CI:0.7-2.23) (Table 6).

Alleles and genotypes	Number of examined alleles and genotypes				Xi2	p	RR	-95%CI	+ 95%CI	OR	-95%CI	+95%CI
	Mild ronchopathy		Moderate ronchopathy									
	n	%	n	%								
Arg	96	71,64	53	71,62	0,00	0,64	1,00	0,65	1,55	1,00	0,53	1,89
Pro	38	28,36	21	28,38	0,00	0,36	1,00	0,45	2,21	1,00	0,53	1,89
Arg /Arg	36	53,73	20	54,05	0,00	0,65	0,99	0,57	1,74	0,99	0,44	2,22
Arg / Pro	24	35,82	13	35,14	0,00	0,64	1,02	0,57	1,83	1,03	0,45	2,36
Pro/ Pro	7	10,45	4	10,81	0,00	0,65	0,97	0,38	2,43	0,96	0,27	3,47

Table 6

It should be emphasized that when comparing the frequency distribution of alleles and genotypes of this locus in patients with ronchopathy, we did not find significant differences from healthy individuals (p > 0.05) (Table 6).

Alleles and genotypes	Number of examined alleles and genotypes				Xi2	p	RR	-95%CI	+ 95%CI	OR	-95%CI	+95%CI
	Mild ronchopathy		Control group									
	n	%	n	%								
Arg	96	71,64	159	78,71	2,2	0,47	0,91	0,53	1,58	0,68	0,41	1,13
Pro	38	28,36	43	21,29	2,20	0,53	1,10	0,71	1,71	1,46	0,89	2,42
Arg /Arg	36	53,73	64	63,37	1,55	0,46	0,85	0,41	1,75	0,67	0,36	1,26
Arg / Pro	24	35,82	31	30,69	0,48	0,38	1,17	0,55	2,47	1,26	0,66	2,42
Pro/ Pro	7	10,45	6	5,94	1,15	0,39	1,76	0,61	5,08	1,85	0,60	5,68

Table 7

Alleles and genotypes	Number of examined alleles and genotypes				Xi2	p	RR	- 95%CI	+ 95%CI	OR	- 95%CI	+ 95%CI
	Moderate ronchopathy		Control group									
	n	%	n	%								
Arg	53	71,62	159	78,71	1,53	0,33	0,91	0,40	2,08	0,68	0,37	1,25
Pro	21	28,38	43	21,29	1,53	0,67	1,10	0,76	1,59	1,47	0,80	2,68
Arg /Arg	20	54,05	64	63,37	0,99	0,31	0,85	0,29	2,50	0,68	0,32	1,46
Arg / Pro	13	35,14	31	30,69	0,25	0,26	1,15	0,37	3,51	1,22	0,55	2,71
Pro/ Pro	4	10,81	6	5,94	0,96	0,26	1,82	0,37	8,97	1,92	0,52	7,09

Table 8

When comparing the frequencies of alleles and genotypes of the rs1800471 polymorphism of the TGFb1 gene, the frequency of the unfavorable Pro allele and the Arg/Pro genotype was determined with a not very high frequency in the subgroup of patients with mild ronchopathy compared to the control sample (Table 7).

In patients with ronchopathy, the frequency of the unfavorable Pro allele is more than 1.5 times insignificantly higher than in the control group (χ^2 = 2.2; P = 0.5; OR = 1.5; 95% CI: 0.89 - 2.42).

Here we can assume a tendency to an increase in the frequency of the unfavorable Pro allele and the Pro/Pro genotype in patients with mild degree of ronchopathy.

The proportion of carriers of the heterozygous genotype Arg/Pro among the representatives of this subgroup and control corresponded to 22.9% and 11.5%, respectively (χ^2 = ; P = ; RR = ; 95% CI; OR = 2.3; 95% .CI). Here it is definitely necessary to note. that the degree of difference is at the level of static insignificance.

Alleles and genotypes	Number of examined alleles and genotypes				Xi2	p	RR	- 95%CI	+ 95%CI	OR	-95%CI	+95%CI
	Mild ronchopathy		Moderate ronchopathy									
	n	%	n	%								
Arg	96	71,64	53	71,62	0,00	0,64	1,00	0,65	1,55	1,00	0,53	1,89
Pro	38	28,36	21	28,38	0,00	0,36	1,00	0,45	2,21	1,00	0,53	1,89
Arg /Arg	36	53,73	20	54,05	0,00	0,65	0,99	0,57	1,74	0,99	0,44	2,22
Arg / Pro	24	35,82	13	35,14	0,00	0,64	1,02	0,57	1,83	1,03	0,45	2,36
Pro/ Pro	7	10,45	4	10,81	0,00	0,65	0,97	0,38	2,43	0,96	0,27	3,47

Table 9

Alleles and genotypes	Number of examined alleles and genotypes				Xi2	p	RR	- 95%CI	+ 95%CI	OR	- 95%CI	+ 95%CI
	Mild ronchopathy		Control group									
	n	%	n	%								
Arg	96	71,64	159	78,71	2,2	0,47	0,91	0,53	1,58	0,68	0,41	1,13
Pro	38	28,36	43	21,29	2,20	0,53	1,10	0,71	1,71	1,46	0,89	2,42
Arg /Arg	36	53,73	64	63,37	1,55	0,46	0,85	0,41	1,75	0,67	0,36	1,26
Arg / Pro	24	35,82	31	30,69	0,48	0,38	1,17	0,55	2,47	1,26	0,66	2,42
Pro/ Pro	7	10,45	6	5,94	1,15	0,39	1,76	0,61	5,08	1,85	0,60	5,68

Table 10

Alleles and genotypes	Number of examined alleles and genotypes				Xi2	p	RR	- 95%CI	+ 95%CI	OR	- 95%CI	+ 95%CI
	Moderate ronchopathy		Control group									
	n	%	n	%								
Arg	53	71,62	159	78,71	1,53	0,33	0,91	0,40	2,08	0,68	0,37	1,25
Pro	21	28,38	43	21,29	1,53	0,67	1,10	0,76	1,59	1,47	0,80	2,68
Arg /Arg	20	54,05	64	63,37	0,99	0,31	0,85	0,29	2,50	0,68	0,32	1,46
Arg / Pro	13	35,14	31	30,69	0,25	0,26	1,15	0,37	3,51	1,22	0,55	2,71
Pro/ Pro	4	10,81	6	5,94	0,96	0,26	1,82	0,37	8,97	1,92	0,52	7,09

Table 11

It should be noted that allelic and genotypic variants of rs1800471 of the TGFb1 gene among patients with ronchopathy of relative severity and in the control sample, as well as in subgroups of mild and moderate severity, are evenly distributed, the differences found did not reach a statistically significant level (p > 0.05) (Table 9-11).

According to our data, the polymorphism of rs1800471 of the TGFb1 gene, according to our data, is an unfavorable variant of

Arg/Pro (associated with overproduction of the proinflammatory cytokine TGFb1), which may make a certain contribution to the formation of impaired nasal breathing and the development of ronchopathy.

Conclusion

Thus, the obtained population genetic data on the rs1800471 polymorphism of the TGFb1 gene also turned out to be representative.

For an unambiguous assessment of the role of the rs1800471 polymorphism of the TGFb1 gene in the formation of impaired nasal breathing and the development of ronchopathy, we believe that additional and in-depth studies are necessary with an increase in the number of patients and control.

It is interesting to note that the adverse effect of this genotype was observed exclusively in patients with ronchopathy, while in patients with ronchopathy, the frequency of this genotype did not differ in comparison with the control group, i.e. there is a significant tendency to an increase in the genotype with an increase in the severity of the pathology. Since this work is one of the few works on the study of the relationship between rs1800471 of the TGFb1 gene and the risk of developing ronchopathy, our data may become the subject of further discussions.

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