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Do *TRIB1* and *IL-9* Gene Polymorphisms Impact the Development and Manifestation of Pituitary Adenoma?

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Abstract. *Background/Aim: To evaluate the association between TRIB1(rs6987702) and IL-9(rs1859430, rs2069870) genotypes with the development and manifestation of pituitary adenoma (PA). Materials and Methods: The study group included 141 patients with PA and the control group consisted of 287 healthy people. The genotyping of rs6987702, rs1859430 and rs2069870 was carried out using a real-time polymerase chain reaction. Results: Statistically significant results were obtained regarding the rs1859430, but there were no significant results regarding rs6987702. We found that the rs1859430 A/A genotype increased the odds of having recurrent PA six times (p=0.006) under the co-dominant model and four times (p=0.021) under the recessive model. Furthermore, the analysis showed that the G/A genotype increased the odds of having recurrent PA 2.3 times (p=0.003) under the co-dominant model, while G/A and A/A genotypes increased the odds 2.7 times (p=0.011) under the over-dominant model. Conclusion: Certain genotypes of rs1859430 can be associated with PA recurrence.*

Pituitary adenoma (PA) is a benign pituitary gland tumor, which starts from the cells of adenohypophysis (1). PAs are mainly inactive, but certain types of PAs secrete hormones and become clinically apparent (2). They can also be classified according to their size: microadenomas, which are more commonly found in female and <60 years old patients, and macroadenomas, which are more prevalent in male and >60 years old patients (3-5).

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Key Words: Pituitary adenoma, *TRIB1* rs6987702 gene polymorphism, IL-9 rs1859430, rs2069870 gene polymorphism, recurrence.

According to the latest statistical report of Central Brain Tumor Registry of the United States (CBTRUS), the incidence rate of benign pituitary tumors has increased, and currently they present 16.4% of all primary brain and central nervous system tumors (6). The report of Brain Tumor Register of Japan published in 2017 showed that pituitary gland was a primary location for 22.6% of all brain tumors and 91.1% of them were benign (7). Meta-analysis of 143 studies showed that the recurrence rate depends on the type of PA (8) and varies from 5% to 16% (7).

Although the exact mechanism of PA development is still unknown, it may include various immunogenetic factors. Many potential molecular markers, which might be involved in the tumorigenesis of PAs, are currently under investigation. In the present study, one TRIB1 gene polymorphism and two *IL-9* gene polymorphisms were selected for further investigation.

Tribbles-1 (TRIB1) is a protein, encoded by the *TRIB1* gene, most commonly found in the nucleus of a cell. This protein belongs to a group of pseudokinases, which consist of 3 different domains: N-terminal PEST domain, pseudokinase domain and C-terminal COP1 binding peptide domain. TRIB kinases have unique sequences located at the C-terminal end (9). Tribbles-1 is mostly found in myeloid cells. It is thought to be important in intracellular signaling, and thereby, to participate in the management of cell cycle, differentiation, metabolism and proliferation, migration and invasion (9-11).

TRIB1 is thought to have oncogenic properties. Miyajima *et al.* (12) have found that TRIB1 inhibits the activity of the tumor suppressor protein p53 by disrupting its binding to the DNA and thereby promoting uncontrolled cell proliferation. The increased expression of the TRIB1 gene is associated with the etiology of breast, ovarian and thyroid cancer (9) and more aggressive form of hepatocellular carcinoma (13). Changes in the TRIB1 gene are associated with certain malignancies in the body. It is thought that TRIB1 gene amplification on chromosome 8 is associated with acute myeloid leukemia (10-11, 14-16).

IL-9 (formerly known as P40) is a 14 kDa glycoprotein composed of 144 amino acids (17). The gene encoding

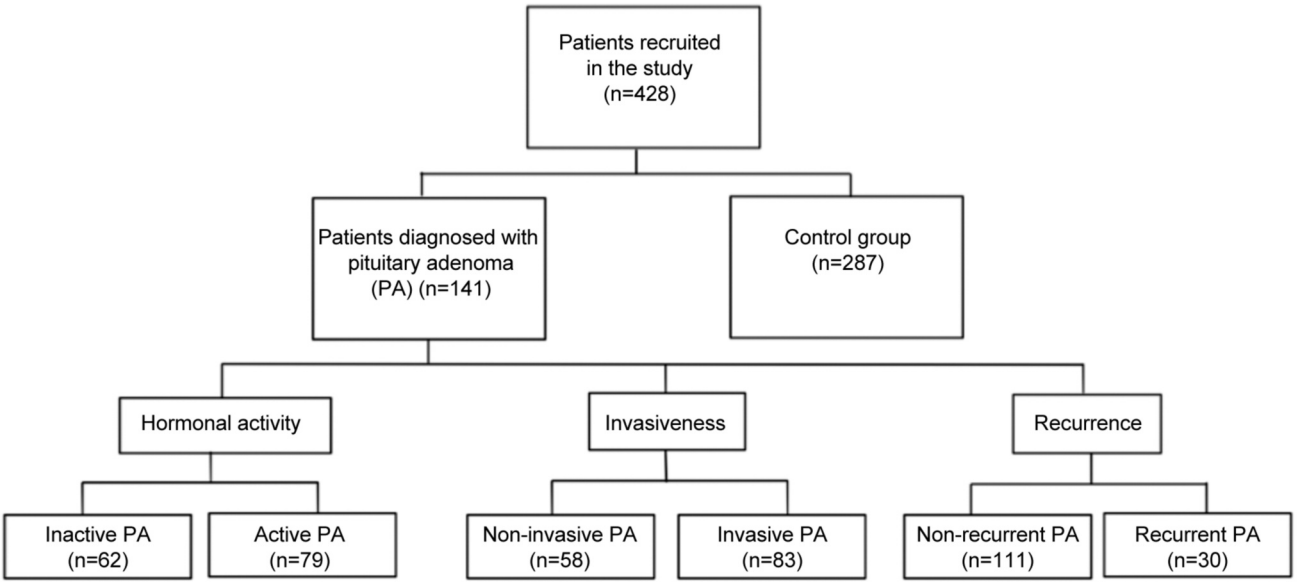

Figure 1. *Patient flow chart*.

human IL-9 is localized on chromosome 5q31-35 (18, 19). It is known, that IL-9 can be secreted by Th1, Th2, Th17 and Th9 lymphocytes and Treg cells (18).

IL-9 production has been shown to be stimulated by TGF-β, IL-4 and IL-2 and inhibited by IFNγ (17). IL-9 is known to have a broad action potential and play an important role in the development of various autoimmune and inflammatory diseases (17, 20-24).

The role of IL-9 in oncology has been extensively studied. It has been shown, that IL-9 contributes to the control of tumor growth (19, 25, 26). It is because this cytokine activates the production of CCL20, which into the foci of the tumor attracts CCR6+ dendritic cells and CCR6+ CD8 lymphocytes, which eradicate tumor cells. IL-9 enhances the cytotoxic effect of mastocytes, prolonging the action of dendritic cells (25, 26). Rivera Vargas *et al*. (26) have found that the *IL-9* rs740002 polymorphism may be associated with an increased risk of melanoma.

Hence, some *TRIB1* and *IL-9* gene polymorphisms may play a role in the tumorigenesis of certain types of cancer. Therefore, in the present study, we investigated whether there is any relationship between the development and clinical manifestation of PA and the polymorphisms s6987702 in the *TRIB1* gene and rs1859430, rs2069870 in the *IL-9* gene.

Materials and Methods

Patients and selection. This study was carried out in the Department of Ophthalmology, Hospital of Lithuanian University of Health Sciences and Laboratory of Ophthalmology, Neuroscience Institute, Lithuanian University of Health Sciences.

Table I. *Demographic characteristics*.

Characteristics	PA, N (%), (n=141)	Control, N (%), (n=287)	*p*-Value
Males, n (%)	54 (38.3)	110 (38.3)	1.0
Females, n (%)	87 (61.7)	177 (61.7)	1.0
Age, median (IQR)	53.0 (22)	52.0 (38)	0.165

PA: Pituitary adenoma; IQR: interquartile rate; *p*-Value: significance level.

This study was approved by the Ethics Committee for Biomedical Research in Lithuanian University of Health Sciences (LUHS) (Number – BE-2-/13). All subjects provided written informed consent in accordance with the Declaration of Helsinki. The study was conducted in the Department of Ophthalmology, Hospital of Lithuanian University of Health Sciences.

Based on our inclusion and exclusion criteria (27), two groups were formed in our study: PA group (n=141) and controls (n=287) (Figure 1).

Evaluation of PAs' hormonal activity, invasiveness, recurrence and DNA extraction and genotyping. The evaluation of PA hormonal activity, invasiveness and recurrence has been described in detail previously (27). DNA extraction and genotyping were based on a real-time polymerase chain reaction (RT-PCR) method (28).

Statistical analysis. Deviation from Hardy-Weinberg equilibrium (HWE) of *TRIB1* (rs6987702) and *IL-9* (rs1859430, rs2069870) genotypes and alleles was evaluated using the Pearson's χ^2 statistical test in the PA and control group.

All categorical variables of TRIB1 (rs6987702) and IL-9 (rs1859430) genotypes and alleles were expressed as absolute

Table II. *The frequency of genotypes and alleles of rs1859430 in patients with PA and control subjects, by gender.*

	IL-9 r*s1859430*					
Genotype	Males		*p*-Value	Females		*p*-Value
	Control group, N (%) (n=110)	PA group, N (%) (n=54)		Control group, N (%) (n=177)	PA group, N (%) (n=87)	
G/G	77 (70.0)[1]	38 (70.4)	1.0	87 (49.2)[1]	52 (59.8)	0.117
G/A	28 (25.5)[2]	14 (29.5)	1.0	72 (40.7)[2]	32 (36.8)	0.593
A/A	5 (4.5)	2 (3.7)	1.0	18 (10.2)	3 (3.4)	0.088
Allele						
G	182 (82.7)[3]	90 (83.3)	0.891	246 (69.5)[3]	136 (78.2)	0.036
A	38 (17.3)[3]	18 (16.7)		108 (30.5)[3]	38 (21.8)	

PA: Pituitary adenoma; IL-9: Interleukin 9; p value: significance level; [1]p=0.001; [2]p=0.011; [3]p=0.001.

numbers with percentages in brackets and compared using the Pearson's χ^2 and Fisher's exact test (when N is less than 50) in both groups. The age of study participants was presented as median and interquartile range (IQR). It was compared between both study groups using the nonparametric Mann-Whitney *U*-test. Binomial logistic regression analysis was performed as reported previously (29). Odds ratios (ORs) with 95% confidence intervals (CIs) were also presented. The lowest values of Akaike information criterion (AIC) showed the best genetic models. Statistically significant difference was indicated when $p<0.05$.

Results

The study group involved 141 patients with pituitary adenoma (PA): 54 males and 87 females. The median age of the study group was 53.0 years. The control group consisted of 287 subjects: 110 males and 177 females; the median age was 52.0 years (p=0.165) (Table I).

The frequency of genotypes and alleles of rs6987702, rs1859430 and rs2069870 in patients with PA and control subjects. The *IL-9* rs2069870 polymorphism deviated from Hardy-Weinberg equilibrium (HWE) ($p<0.05$). Hence, this polymorphism was not included in our further statistical analysis.

The genotyping of *IL-9* rs1859430 and *TRIB1* rs6987702 was performed successfully, and this time the genotype distribution did not deviate from Hardy-Weinberg equilibrium (HWE) ($p>0.05$).

Statistical analysis of genotype and allele distributions did not reveal any statistically significant differences between the study and control groups.

Binary logistic regression was performed to assess the impact of rs6987702 and rs1859430 on PA development, but the results did not show any significant difference.

The frequency of genotypes and alleles of rs6987702 and rs1859430 in patients with PA and control subjects, by gender. We performed additional statistical analysis considering the gender of study participants in the study and control groups. Unfortunately, the results did not reveal any associations between the rs6987702 and PA neither in males, nor in females.

Statistically significant results were found in the control group, while searching for the association between the rs6987702 and PA. The homozygote G/G genotype was more frequent in healthy males than in healthy females (70.0% *vs*. 49.2%, respectively; p=0.001). The heterogygote G/A genotype was more frequent in healthy females than in healthy males (40.7% *vs*. 25.5%, respectively; p=0.011) (Table II).

The A allele was also more frequent in healthy females than in healthy males (30.5% *vs*. 17.3%; $p\leq$00.001). However, the G allele was more frequent in healthy males than in healthy females (82.7% *vs*. 69.5%; $p\leq$0.001).

Binary logistic regression was performed to assess the impact of rs6987702, rs1859430 and gender on PA development, but the results did not show any significant difference.

The frequency of genotypes and alleles of rs6987702 and rs1859430 in patients with PA and control subjects, by PA invasiveness. We also evaluated the impact of rs6987702 and rs1859430 on PA development and its invasiveness. Unfortunately, the results did not reveal any associations of the rs6987702 and rs1859430 with the invasiveness or non-invasiveness of PA.

Binary logistic regression was performed to assess the impact of rs6987702 and rs1859430 on PA invasiveness and non-invasiveness, but the results did not show any significant difference.

The frequency of genotypes and alleles of rs6987702 and rs1859430 in patients with PA and control subjects, by PA hormonal activity. The distribution of genotypes and alleles of rs6987702 and rs1859430 was evaluated in patients with PA, while considering the hormonal activity of the benign

Table III. *The frequency of genotypes and alleles of rs6987702 and rs1859430 in control subjects and patients with PA, by PA recurrence.*

		Frequency (%)					
Polymorphism	Genotype/ allele	PA without recurrence group, N (%) (n=111)	Control group, N (%) (n=287)	*p*-Value	PA with recurrence group, N (%) (n=30)	Control group, N (%) (n=287)	*p*-Value
TRIB1	Genotype						
r*s6987702*	T/T	58 (52.3)	150 (52.3)	0.998	15 (50)	150 (52.3)	0.85
	T/C	48 (43.2)	110 (38.3)	0.369	14 (46.7)	110 (38.3)	0.433
	C/C	5 (4.5)	27 (9.4)	0.107	1 (3.3)	27 (9.4)	0.495
	Allele						
	T	164 (73.9)	410 (71.4)	0.490	44 (70.3)	410 (71.4)	0.881
	C	58 (26.1)	164 (28.6)		16 (29.7)	164 (28.6)	
IL-9	Genotype						
r*s1859430*	G/G	78 (70.3)[1]	185 (64.5)	0.272	12 (40)[1]	185 (64.5)	0.010
	G/A	32 (28.8)	92 (32.1)	0.533	14 (46.7)	92 (32.1)	0.153
	A/A	1 (0.9)[2]	10 (3.5)	0.159	4 (13.3)[2]	10 (3.5)	0.034
	Allele						
	G	188 (84.7)[3]	462 (80.5)	0.170	38 (63.3)[3]	462 (80.5)	0.004
	A	34 (15.3)[3]	112 (19.5)		22 (36.7)[3]	112 (19.5)	

PA: Pituitary adenoma; IL-9: interleukin 9; *p*-value=significance level; [1]p=0.005; [2]p=0.007; [3]p=0.001.

tumour of pituitary gland. Unfortunately, we did not find any associations between these two polymorphisms and hormonally active or inactive PA development.

Binary logistic regression was also performed in order to evaluate the impact of rs6987702 and rs1859430 on active PA and inactive PA development, but the results did not reveal any statistically significant association.

The frequency of genotypes and alleles of rs6987702 and rs1859430 in patients with PA and control subjects by PA recurrence. The distribution of genotypes and alleles of rs6987702 and rs1859430 was evaluated in patients with PA by PA hormonal activity. Unfortunately, we found no associations between rs6987702 and active PA or inactive PA development.

In the genotype and allele analysis of rs1859430, we found statistically significant differences regarding the genotype G/G (70.3% *vs*. 40%, p=0.010), A/A (0.9% *vs*. 13.3%, p=0.034) and allele G (84.7% *vs*. 63.3%), A (15.3% *vs*. 36.7%) (p=0.004) distribution between the PA without recurrence and PA with recurrence groups (Table III).

Binary logistic regression analysis of only rs1859430 revealed statistically significant results (Tables IV and V).

Discussion

To our knowledge, *TRIB1* (rs6987702) and *IL-9* (rs1859430, rs2069870) gene polymorphisms association with pituitary adenoma was analysed for the first time. In our study, *IL-9* rs2069870 polymorphism deviated from Hardy-Weinberg equilibrium (p<0.05) and thus was excluded from further analysis. We found that the *IL-9* rs1859430 was associated with PA development; unfortunately, we did not find any associations with the *TRIB1* (rs6987702) gene polymorphism. There are many others studies analyzing associations of the same gene polymorphisms with others types of tumours (30-37) and the oncogenic properties of TRIB1 have been shown in numerous studies (30-37). TRIB1 has been identified as an oncogene in acute myeloid leukemia (30), prostate cancer (31), colon and rectal cancer (32), gastric cancer (33), malignant mesothelioma (34), esophageal carcinoma (35), ovarian cancer (36), and thyroid cancer (37). Liang *et al*. (15) have suggested that 8q24 is significantly associated with human cancers and this region may carry oncogenes related to tumorigenesis and/or progression. TRIB1, which belongs to the Trib family, is classified as pseudokinase and has important roles in many cellular processes associated with tumors development.

Our analysis revealed that the G/G genotype and G allele of the *IL-9* (rs1859430) polymorphism are more prevalent among patients with a recurrent PA. Moreover, our results show the that A/A genotype and A allele are significantly more common among those patients, whom PA did not reoccur. We can hypothesize that IL9 can be important for PA recurrence but it has no impact on hormonal activity or invasiveness.

Besides the role of IL-9 in immune responses, its growth factor and antiapoptotic activities on multiple transformed cells suggest a potential role in hematological malignancies (38). Chruszcz *et al*. (39) have stated, that Interleukin 9

Table IV. *Binary logistic regression analysis of rs6987702 in control subjects and patients with PA with or without recurrence.*

Model	Genotype	OR (95%CI)	*p*-Value	AIC
TRIB1 r*s6987702*				
PA without recurrence				
Co-dominant	T/T	1		471.990
	T/C	1.129 (0.716-1.778)	0.602	
	C/C	0.479 (0.176-1.303)	0.150	
Dominant	T/T	1		473.157
	T/C+C/C	1.001 (0.645-1.551)	0.998	
Recessive	T/T+T/C	1		470.262
	C/C	0.454 (0.170-1.211)	0.115	
Over-dominant	T/T+C/C	1		472.354
	T/C	1.226 (0.786-1.912)	0.369	
Additive	---	0.885 (0.625-1.254)	0.493	472.683
PA with recurrence				
Co-dominant	T/T	1		200.589
	T/C	1.273 (0.590-2.745)	0.539	
	C/C	0.370 (0.047-2.921)	0.346	
Dominant	T/T	1		200.473
	T/C+C/C	1.095 (0.516-2.323)	0.813	
Recessive	T/T+T/C	1		198.965
	C/C	0.332 (0.044-2.535)	0.288	
Over-dominant	T/T+C/C	1		199.749
	T/C	1.408 (0.661-2.998)	0.375	
Additive	---	0.912 (0.506-1.645)	0.760	200.435

OR: Odds ratio; CI: confidence interval; AIC: Akaike information criterion; *p*: significance level.

Table V. *Binary logistic regression analysis of rs1859430 in control subjects and patients with PA with or without recurrence.*

Model	Genotype	OR (95%CI)	*p*-Value	AIC
IL-9 r*s1859430*				
PA without recurrence				
Co-dominant	G/G	1		472.090
	G/A	0.825 (0.510-1.335)	0.433	
	A/A	0.237 (0.030-1.884)	0.174	
Dominant	G/G	1		471.935
	G/A+A/A	0.767 (0.478-1.232)	0.273	
Recessive	G/G+G/A	1		470.711
	A/A	0.252 (0.032-1.991)	0.191	
Over-dominant	G/G+A/A	1		472.765
	G/A	0.859 (0.531-1.387)	0.533	
Additive	---	0.737 (0.480-1.131)	0.163	471.139
PA with recurrence				
Co-dominant	G/G	1		193.911
	G/A	2.346 (1.043-5.277)	0.039	
	A/A	6.167 (1.684-22.587)	0.006	
Dominant	G/G	1		193.863
	G/A+A/A	2.721 (1.260-5.872)	0.011	
Recessive	G/G+G/A	1		196.147
	A/A	4.262 (1.249-14.540)	0.021	
Over-dominant	G/G+A/A	1		198.038
	G/A	1.855 (0.868-3.961)	0.111	
Additive	---	2.435 (1.359-4.365)	0.003	191.928

PA: Pituitary adenoma; IL-9: interleukin 9; OR: odds ratio; CI: confidence interval; AIC: Akaike information criterion; *p*: significance level.

facilitates an immunosuppressive environment to promote tumor growth or to restrain tumor progression based on tumor type. IL-9 also substantially contributes to the proliferation and migration of lung cancer cells while helping them escape apoptosis (40). Similar biological functions of IL-9 have been also observed in breast cancer, colon carcinoma (39), and hematopoietic malignancies (41). It is thought that IL-9 is strongly associated with tumor progression; thus, blocking IL-9 may be an applicable strategy for tumor treatment (42). The IL-9 receptor is a member of the hematopoietic receptor superfamily and is expressed in membrane-bound and soluble forms (43). IL-9 in malignant tumors is almost exclusively related to Hodgking's lymphoma and anaplastic large cell lymphomas (44, 45). Also, the functional role of IL-9 has been proven in experimental human and animal studies. *Hoelzinger et al*. (39) results show the ability of IL-9 to function as an inhibitor of adaptive immunity that prevents the formation of immunologic memory to a growing tumor, highlighting the potential for IL-9 neutralization as a unique tool for cancer immunotherapy.

IL-9 is also known to be involved in mast cell differentiation and T-cell lymphoma oncogenesis in mice (46). Notably, IL-9 overexpression induces thymic lymphomas in mice, and IL-9 production has an effect on Hodgkin's disease and human T-lymphotropic virus type I (HTLV-I)-transformed T cells in humans. IL-9 activities also involve IL-2, -4, -7, -15 and -21 signaling, which is mediated by a specific receptor chain that forms a heterodimeric receptor with the common γ chain (47). The IL-9R and common γ chains associate with Janus kinase (JAK) 1 and JAK3 and trigger the signal transducer and activator of transcription (STAT)-1, -3 and -5, insulin receptor signaling (IRS) and RAS-mitogen-activated protein kinase (MAPK) pathways. In addition, IL-9 is not expressed by Th 2 and 9 cells in the absence of STAT6 expression. Dysregulated IL-9 response also leads to autonomous cell growth and the malignant transformation of lymphoid cells associated with constitutive activation of the JAK/STAT pathway *in vitro* (48).

There are few limitations in this study. First, functional studies were not performed in the present study in order to confirm the association between the chosen SNPs and the

development and clinical manifestation of PA. Second, the sample size of control subjects in our study was comparatively small. Despite these limitations, a thorough clinical examination of the patients can be considered as the strength of our study. Prior to our study, all the patients were consulted by a general practitioner, and patients with systemic infectious and noninfectious diseases, such as malignant tumors, rheumatoid diseases, and end-stage liver or renal diseases, were excluded from the study.

To conclude, a possible association between rs1859430 and the recurrence of PA has been found. However, additional studies are needed to support our findings.

Conflicts of Interest

None of the Authors have any conflict of interest regarding this study.

Authors' Contributions

RL, LK and BG performed the Ophthalmological evaluation. TM and AV carried out the genotyping. TM performed the statistical analysis and drafted the manuscript. BG participated in the design of the study and RL conceived the study, participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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