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TBX15 rs98422, *DNM3* rs1011731, *RAD51B* rs8017304, and rs2588809 Gene Polymorphisms and Associations With Pituitary Adenoma

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Abstract. *Background: Pituitary adenoma (PA) is a benign tumor of parenchymal cells in the adenohypophysis, and it's development is strongly associated with genetic factors.This study aim was to find whether TBX15 rs98422, DNM3 rs1011731, RAD51B rs8017304, and rs2588809 single nucleotide polymorphisms can be associated with pituitary adenoma. While the TBX15 gene belongs to the T-box family of genes and is a transcription factor involved in many developmental processes, the DNM3 encodes a protein that is a member of the dynamin family with mechanochemical properties involved in actin-membrane processes, predominantly in membrane budding, and the RAD51B gene plays a significant role in homologous recombination in DNA repair for genome stability. Materials and Methods: The study enrolled 113 patients with pituitary adenoma and 283 healthy control subjects. DNA samples were extracted and purified from peripheral blood leukocytes. Genotyping was carried out using real-time polymerase chain reaction. The results were assessed using binomial logistic regression. Results: Our study revealed that RAD51B rs2588809 TT genotype could be associated with PA development in the co-dominant (OR=6.833; 95% CI=2.557-18.262; p<0.001) and recessive (OR=7.066; 95% CI=2.667-18.722; p<0.001) models. The same results were observed in females but not in males and PA without recurrence, while in PA with recurrence, no statistically significant results were obtained. Conclusion: RAD51B rs2588809 TT genotype may increase the odds of PA development in women; it may also be associated with non-recurrent PA development.*

Pituitary adenoma (PA) is an intracranial tumor localized in the bone cavity (*sella turcica*) surrounded by multiple neural, vascular, endocrine, and bone structures, which further may contribute to an assortment of tumor types (1-7). PA accounts for approximately 15 to 20 percent of primary brain tumors with a prevalence of 77.6-97.6 PA cases per 100,000 individuals. Clinically significant PAs occur in one out of 1064 individuals (5-11). PA can occur insidiously – most patients do not realize they have it until specifically investigated. This tumor can manifest in two ways: an endocrine imbalance or pressure on the surrounding structures. The latter is the most common form of macroadenoma manifestation (12). Six to ten percent of all PAs expand into the cavernous sinus (13, 14). The optic chiasm is directly above the pituitary gland, so a prolonged compression of the chiasm can cause primary optic nerve atrophy and result in visual function defects, such as decreased visual acuity and visual field defects or impaired color vision (15). The earlier the tumor is diagnosed, the more likely it is to be removed and the visual function to be preserved. Endocrine changes may be due to the overexpression of tumor hormones or hypoexpression, when the tumor compresses the pituitary gland (16).

The etiology and pathogenesis of PA are complex and still poorly understood. PA represents a heterogeneous disease whose pathogenesis is a multifactorial process that involves both environmental and genetic factors. Therefore, a better understanding of the PA pathogenesis requires a comprehensive research of this disease's biological and genetic markers. Plenty of possible molecular markers, as well as intelrleukin 9 variant rs1859430, which might be incorporated in the tumorogenesis of PAs, are currently under investigation (17). Recent studies focus on genetic

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Table I. *Characteristics of study subjects.*

Characteristics	Subjects with PA (group I) n=113	Control group (group II) n=283	*p*-Value
Men, n (%)	45 (39.8)	100 (35.3)	0.438
Women, n (%)	68 (60.2)	183 (64.7)	
Age, median (IQR)	54 (22.5)	55.5 (27)	0.426

markers for cancer development, so we aimed to elucidate the role of four *TXB15, DNM3* and *RAD51B* single nucleotide variants in PA development. The elevated genes has been reported in a variety of cancers, including prostate, ovarian cancers. However, the data regarding *TBX15, DNM3* and *RAD51B* genes and PA is still lacking (18-20).

TBX15, a T-box family member, is possibly involved in cancer cell transformation because of its antiapoptotic function (18). It also is known that T-box genes are involved in in carcinogenesis (21-23). *TBX15* is associated with prostate (24), thyroid cancer (19, 25, 26), ovarian carcinoma (20).

The other marker dynamin 3 (*DNM3*) is a candidate tumor suppressor gene. This gene encodes a member of the dynamin family, which possesses mechanochemical properties to tabulate and sever membranes (27). However, few reports describe the relationship between *DNM3* and malignant diseases (28, 29). *DNM3* has been found mainly in the brain (at a lower level than *DNM1*) and testicles, and less frequently in the lungs and heart (30). The importance of the *DNM3* gene has been investigated in gliomas (31, 32), hepatocellular carcinoma (33-35), colon cancer (36), and papillary thyroid carcinoma (37). Few studies have investigated the association between DNM3 and hepatocellular carcinoma, breast cancer, T-cell lymphoma, colon cancer (28-30, 33-34, 38, 39). Additionally, the importance of DNM3 was investigated in brain tumors glioblastomas (31-32).

RAD51B plays a role in homologous DNA pairing and strand exchange in DNA double-strand break repair (38, 40). The importance of RAD51B has previously been investigated in the breast, ovarian, lung cancer and uterine leiomyomas (31, 41-43). Also, some studies have been carried out to look for the possible association between the RAD51 gene variants and pancreatic (44-47), prostate cancer (48, 49), malignant melanoma (50), colorectal adenocarcinoma (51), endometrial cancer (52), soft tissue sarcoma (53) and glioblastoma (54).

Our study aimed to determine associations between *TBX15* rs98422, *DNM3* rs1011731, *RAD51B* rs8017304, rs2588809 single nucleotide polymorphisms and pituitary adenoma invasiveness, development, and recurrence.

These findings support the hypothesised role of *TBX15* , DNM3 and RAD 51 as tumour promoters. Based on the TBX15, DNM3 and RAD51B associations with cancerous processes we selected four widely described SNPs located in these genes. According to the dbSNP database (https://www.ncbi.nlm.nih.gov/snp/) the minor allele frequencies of these intronic variants (*TBX15* rs984222, *DNM3* rs1011731, *RAD51B* rs8017304, rs2588809) are more than 0.1 in the Europe population, and none of these variants have been studied with PA development, invasiveness, PA activity and recurrence. The aim of the present study was to determine these associations.

Materials and Methods

Patients and selection. This study was carried out at the Department of Ophthalmology, Hospital of Lithuanian University of Health Sciences and Laboratory of Ophthalmology, Neuroscience Institute, Lithuanian University of Health Sciences. The Ethics Committee for Biomedical Research at Lithuanian University of Health Sciences (LUHS) approved the study (number BE-2-47). All subjects provided written informed consent under the Declaration of Helsinki. Based on our inclusion and exclusion criteria (55), two groups were formed in the study: the PA group (*n*=113) and the control group (*n*=283).

Evaluation of PA hormonal activity, invasiveness, recurrence and DNA extraction and genotyping. The analysis of all pituitary adenomas was based on histopathological findings of PA and hormone levels in the blood serum before surgery. All PA subjects were categorized into two groups – active and inactive PA (56).

Since some of the subjects had already had surgery in recent years, we categorized them by recurrence of pituitary adenoma into two groups – PA with and without recurrence.

Pituitary adenoma recurrence was diagnosed when enlargement of a residual tumor or a new growth was documented on follow-up magnetic resonance imaging (MRI) after surgical resection during the period of this study. The residual tumor was considered stable if there no signs of tumor progression on follow-up MRI. Most prolactinomas were surgically treated because of the remaining pressure effects of surrounding structures or ineffective medical treatment.

PA invasiveness has been described previously (55). The suprasellar extension and sphenoid sinus invasion by PA were classified according to the Hardy classification modified by Wilson, and the degree of suprasellar and parasellar extensions was graded as stages A–E. The degree of sellar floor erosion was graded as grades I-IV. Grade III shows localized sellar perforation, and grade IV shows diffuse destruction of sellar floor, which are the signs of invasive PA. The Knosp classification system was used to quantify the invasion of the cavernous sinus. Grade 3 and 4 pituitary tumors were considered to be invasive.

DNA was extracted from 200 μL venous blood (white blood cells) using the silica-based membrane technology utilizing a genomic DNA extraction kit (GeneJET Genomic DNA Purification Kit, Thermo Scientific, MA, USA), according to the manufacturer's recommendations. The genotyping of *TBX15* rs984222, *DNM3* rs1011731, *RAD51B* rs8017304 and rs2588809 was carried out using the real-time PCR. SNPs were genotyped on the Step One Plus real-time PCR system (Applied Biosystems, Foster City, CA, USA). The TaqMan® SNP genotyping assays (Thermo Scientific) for all SNPs were performed according to the manufacturer's protocol. The Allelic Discrimination program was used during the

Table II. *TBX15 rs984222, DNM3 rs1011731, RAD51B rs8017304 and RAD51B rs2588809 genotype and allele frequencies in the PA patient and control groups.*

SNP	Genotype/ allele	Group		*p*-Value
		Control group n=283 n (%)	PA group n=113 n (%)	
TBX15	Genotype			
rs984222	G/G	141 (49.8)	65 (57.5)	
	G/C	120 (42.4)	42 (37.2)	0.341
	C/C	22 (7.8)	6 (5.3)	
	In total	283 (100)	113 (100)	
	Allele			
	G	402 (71.02)	172 (76.11)	0.148
	C	164 (28.98)	54 (23.89)	
DNM3	Genotype			
rs1011731	A/A	90 (31.8)	34 (30.1)	
	G/A	142 (50.2)	57 (50.4)	0.919
	G/G	51 (18.0)	22 (19.5)	
	In total	283 (100)	113 (100)	
	Allele			
	G	322 (56.89)	125 (55.31)	0.685
	A	244 (43.11)	101 (44.69)	
RAD51B	Genotype			
rs8017304	AA	130 (45.94)	49 (43.36)	
	AG	116 (40.98)	52 (46.02)	0.609
	GG	37 (13.08)	12 (10.62)	
	In total	283 (100)	113 (100)	
	Allele			
	A	376 (66.43)	150 (66.37)	0.987
	G	190 (33.57)	76 (33.63)	
RAD51B	Genotype			
rs2588809	CC	198 (69.96)	74 (65.49)	
	CT	70 (24.74)	24 (21.24)	0.024
	TT	15 (5.30)	15 (13.27)	
	In total	283 (100)	113 (100)	
	Allele			
	C	466 (82.33)	172 (76.12)	0.045
	T	100 (17.67)	54 (23.88)	

PA: Pituitary adenoma; *p*-Value: Bonferroni corrected level of significance, differences are considered statistically significant when $p<0.05/4$.

real-time PCR. The program determined individual genotypes according to the fluorescence intensity rate of different detectors (VIC and FAM).

Statistical analysis. The age of study participants was presented as the median and interquartile range (IQR). It was compared between both study groups using the nonparametric Mann-Whitney *U*-test. All categorical variables of *TBX15* rs98422, *DNM3* rs1011731, *RAD51B* rs8017304 and rs2588809 genotypes and alleles were expressed as absolute numbers with percentages in brackets and compared using the Pearson's χ^2 and Fisher's exact test (when $n<50$) in both groups. Binomial logistic regression analysis was performed to evaluate the genotype and allele impact on PA development and reported as odds ratios (ORs) with 95% confidence intervals (CIs). The lowest values of the Akaike information criterion (AIC) showed the best genetic models. Statistically significant differences were reported when $p<0.05$, but for multiple comparisons, the Bonferroni correction was applied with the $p<0.05/4$ (since we analyzed four different SNPs).

Table III. *Binary logistic regression analysis of RAD51B rs2588809.*

Model	Genotype	OR (95% CI)	*p*-Value	AIC
		RAD51B rs2588809		
Co-dominant	C/T	0.873 (0.509; 1.497)	0.622	459.716
	T/T	6.833 (2.557; 18.262)	**<0.001**	
Dominant	C/T+T/T	1.332 (0.833; 2.129)	0.232	474.155
Recessive	T/T	7.066 (2.667; 18.722)	**<0.001**	457.963
Overdominant	C/T	0.763 (0.449; 1.298)	0.318	474.546
Additive	T	1.627 (1.135; 2.334)	**0.008**	468.686

OR: Odds ratio; AIC: Akaike information criterion; *p*-Value: Bonferroni corrected level of significance, differences are considered statistically significant when $p<0.05/4$. Significant *p*-Values are shown in bold.

Results

A total of 396 individuals were included in the study. Two groups of subjects were formed during the study. The first one included patients with pituitary adenoma, the second included healthy subjects (control group). The characteristics of the subjects are presented in Table I. The first group consisted of 113 individuals, of whom 45 (39.8%) were men, and 68 (60.2%) were women. The median age of this group was 54 years. The control group consisted of 100 (35.3%) men and 183 (64.7%) women. In total, the control group consisted of 283 individuals with a median age of 55.5 years.

TBX15 rs984222, DNM3 rs1011731, RAD51B rs8017304, and RAD51B rs2588809 genotype frequencies in the pituitary adenoma and healthy population groups. Hardy Weinberg analysis was performed to compare the observed and expected frequencies of *TBX15* rs984222, *DNM3* rs1011731, *RAD51B* rs8017304, and *RAD51B* rs2588809 using the χ^2 test in the control group. The genotype distribution of the polymorphisms matched the Hardy-Weinberg equilibrium. ($p>0.001$) (57). *TBX15* rs984222, *DNM3* rs1011731, *RAD51B* rs8017304, and *RAD51B* rs2588809 genotypes and allele frequencies did not significantly differ between the PA and control groups. The results are shownin Table II.

Binomial logistic regression analysis was performed to estimate the impact of genotypes and alleles on PA development. Binomial logistic regression analysis of *RAD51* rs2588809 revealed that the TT genotype was associated with about 7-fold increased odds of PA development in the co-dominant (OR=6.833; 95% CI=2.557-18.262; $p<0.001$) and recessive (OR=7.066; 95% CI=2.667-

Table IV. *TBX15 rs984222, DNM3 rs1011731, RAD51B rs8017304 and RAD51B rs2588809 genotype and allele frequencies in PA patients and controls by gender.*

Genotype/allele	Males		*p*-Value	Females		*p*-Value
	PA group n=45 n (%)	Control group n=100 n (%)		PA group n=68 n (%)	Control group n=183 n (%)	
			TBX15 rs984222			
GG	25 (55.6)	45 (45.0)	0.499	40 (58.8)	96 (52.5)	0.532
GC	17 (37.8)	47 (47.0)		25 (36.8)	73 (39.9)	
CC	3 (6.7)	8 (8.0)		3 (4.4)	14 (7.7)	
Allele						
G	67 (74.4)	137 (68.5)	0.305	105 (77.20)	265 (72.40)	0.277
C	23 (25.6)	63 (31.5)		31 (22.80)	101 (27.60)	
			DNM3 rs10111731			
AA	12 (26.7)	35 (35.0)	0.583	22 (32.4)	55 (30.1)	0.923
AG	25 (55.6)	51 (51.0)		32 (47.1)	91 (49.7)	
GG	8 (17.7)	14 (14.0)		14 (20.6)	37 (20.2)	
Allele						
A	49 (54.4)	121 (60.5)	0.333	76 (55.88)	201 (54.91)	0.847
G	41 (45.6)	79 (39.5)		60 (44.12)	165 (45.09)	
			RAD51B rs8017304			
AA	19 (42.22)	38 (38.0)	0.890	30 (44.12)	92 (50.27)	0.340
AG	19 (42.22)	45 (45.0)		33 (48.53)	71 (38.25)	
GG	7 (15.56)	17 (17.0)		5 (7.35)	20 (11.48)	
Allele						
A	57 (63.33)	121 (60.5)	0.646	93 (68.38)	255 (69.67)	0.780
G	33 (36.67)	79 (39.5)		43 (31.62)	111 (30.33)	
			RAD51B rs2588809			
CC	27 (60.0)	75 (75.0)	0.179	47 (69.12)	123 (67.21)	**0.011**
CT	13 (28.89)	19 (19.0)		11 (16.18)	51 (27.87)	
TT	5 (11.11)	6 (6.0)		10 (14.7)	9 (4.92)	
Allele						
C	67 (74.44)	169 (84.5)	0.042	105 (77.21)	297 (81.15)	0.325
T	23 (25.56)	31 (15.5)		31 (22.79)	69 (18.85)	

PA: Pituitary adenoma; *p*-Value: Bonferroni corrected level of significance, differences are considered statistically significant when $p<0.05/4$. Significant *p*-Values are shown in bold.

18.722; $p<0.001$) models. Each copy of the T allele was associated with increased odds of PA development (OR=1.627; 95% CI=1.135-2.334; $p=0.008$) (Table III). Analysis of *TBX15* rs984222, *DNM3* rs1011731, and *RAD51B* rs8017304 did not show any statistically significant results (Supplementary material).

Comparison of TBX15 rs984222, DNM3 rs101173, RAD51B rs8017304, and rs2588809 polymorphisms in pituitary adenoma patients by gender. Statistical analysis was also performed to compare the *TBX15* rs984222, *DNM3* rs101731, and *RAD51* rs8017304 genotype and allele frequencies between the patients with PA and control group subjects by their gender (Table IV). The analysis of *RAD51B* rs2588809 showed a statistically significant difference in the CC, CT, and TT genotype distributions between females with PA and control females (69.12%, 16.18%, and 14.7% *vs*. 67.21%, 27.87%, and 4.92%, respectively, $p=0.011$). The results are presented in Table IV.

Binominal logistic regression was performed to evaluate these polymorphisms' impact on the PA development in men and women, separately. Binominal logistic regression analysis in the women's group showed that the TT genotype was associated with 6.7-fold higher odds of PA development in

Table V. *Binary logistic regression analysis of RAD51B rs2588809 in females.*

Model	Genotype	OR (95% CI)	*p*-Value	AIC
TBX15 rs984222				
RAD51B rs2588809				
Co-dominant	C/T	0.572 (0.275; 1.188)	0.134	282.117
	T/T	6.744 (2.021; 22.583)	**0.002**	
Dominant	C/T+T/T	1.013 (0.554; 1.852)	0.966	295.251
Recessive	T/T	7.716 (2.331; 25.533)	**0.001**	282.517
Overdominant	C/T	0.486 (0.236; 1.000)	0.050	291.045
Additive	T	1.425 (0.905; 2.245)	0.126	292.969

OR: Odds ratio; AIC: Akaike information criterion; *p*-Value: Bonferroni corrected level of significance, differences are considered statistically significant when $p<0.05/4$. Significant *p*-Values are shown in bold.

the co-dominant model (OR=6.744; 95% CI=2.021-22.583; $p=0.002$) and with 7.7-fold increased odds of PA development in the recessive model (OR=7.716; 95% CI=2.332-25.533; $p=0.001$). The results are shown in Table V. The *TBX15* rs984222, *DNM3* rs1011731, and *RAD51B* rs8017304 were not associated with female PA development (Supplementary material). Also, no statistically significant variables were found in the men's group (Supplementary material).

Association of TBX15 rs984222, DNM3 rs1011731, RAD51B rs8017304, and RAD51B rs2588809 polymorphisms with clinical and morphological features of PA. One of our study's objectives was to determine if there is a relationship between *TBX15*, *DNM3,* and *RAD51B* gene polymorphisms with PA's clinical and morphological features. Comparing the distribution of genotypes and alleles of *TBX15* rs984222, *DNM3* rs1011731, *RAD51B* rs8017304, and *RAD51B* rs2588809 between the PA groups by recurrence and the control group, we obtained statistically significant differences in the rs2588809 CC, CT, and TT genotype distributions between PA without-recurrence patients and healthy controls (67.03%, 17.58% and 15.39% *vs*. 69.96%, 24.73%, and 5.31%, respectively; $p=0.005$). The results are shown in Table VI. Regarding PA recurrence, we performed binominal logistic regression to evaluate the impact of *TBX15* rs984222, *DNM3* rs1011731, *RAD51B* rs8017304, and *RAD51B* rs2588809 polymorphisms on the development of PAs with and without recurrence. We found that the *RAD15B* rs2588809 TT genotype was associated with approximately 8-fold increased odds of development of PA without recurrence in the co-dominant (OR=7.842; 95% CI=2.890-21.277; $p<0.001$) and recessive model (OR=8.394; 95% CI=3.122-22.571; $p<0.001$). Also, each T allele was associated with 1.7-fold increased odds of development of PA without recurrence in the additive model (OR=1.676; 95% CI=0.114-2.457; $p=0.008$). The data are presented in Table VII. No associations were found in the recurrent PA group (Supplementary material). The *TBX15* rs984222, *DNM3* rs1011731, and *RAD51B* rs8017304 were not associated with PA recurrence (Supplementary material).

TBX15 rs984222, *DNM3* rs1011731, *RAD51B* rs8017304, and *RAD51B* rs2588809 genotypes and allele frequencies were compared between the active and inactive PA and healthy control groups. We found that the *RAD51B* rs8017304 G allele was detected significantly more frequently in the inactive PA group *vs*. the control group (48.13% *vs*. 33.57%; $p=0.004$) (Table VIII).

Binominal logistic regression revealed that the *RAD51B* rs2588809 TT genotype was associated with increased odds of active PA development in the codominant (OR=6.058; 95% CI=2.146-19.734; $p=0.001$) and recessive (OR=7.103; 95% CI=2.366-21.320; $p<0.001$) models (Table IX). Also, the *RAD51B* rs2588809 TT genotype was associated with increased odds of inactive PA development in the codominant (OR=7.247; 95% CI=2.29-22.906; $p=0.001$) and recessive (OR=7.260; 95% CI=2.260-21.840; $p=0.001$) models. Each T allele at rs2588809 was associated with 1.9-fold increased odds of inactive PA development in the additive model (OR=1.865; 95% CI=1.154-3.014; $p=0.011$). These data are presented in Table IX. The *TBX15* rs984222, *DNM3* rs1011731 and *RAD51* rs8017304 were not associated with PA hormonal activity (Supplementary material).

We then compared the distribution of *TBX15* rs984222, *DNM3* rs1011731, *RAD51* rs8017304, and rs2588809 genotypes and alleles in patients with invasive and non-invasive PAs *vs*. healthy controls. The *RAD51B* rs2588809 genotypes (CC, CT, and TT) were distributed significantly differently in patients with non-invasive PA and healthy subjects (59.09%, 22.72% and 18.19% *vs*. 69.96%, 24.73%, and 5.31%, respectively, $p=0.008$) (Table X). Also, the T allele occurred more frequently in patients with non-invasive PA than in control subjects (29.55% *vs*. 17.67%, $p=0.008$). The results are presented in Table X.

Binominal logistic regression was performed in patients with PA by its invasiveness. It was revealed that the *RAD51B* rs2588809 TT genotype was associated with about 5-fold increased odds of invasive PA in the codominant (OR=4.881; 95% CI=1.570-15.172; $p=0.006$) and recessive (OR=5.212; 95% CI=1.693-16.050; $p=0.004$) models (Table XI). Also, the *RAD51B* rs2588809 TT genotype was associated with increased odds of non-invasive PA development in the codominant (OR=10.513; 95% CI=3.381-32.688; $p<0.001$) and recessive (OR=10.259; 95% CI=3.368-31.255; $p<0.001$) models. Each T allele was associated with 2.2-fold increased odds of non-invasive PA development in the additive model (OR=2.222; 95% CI=1.352-3.652; $p=0.002$). The results are shown in Table XI. The *TBX15* rs984222, *DNM3* rs1011731, and *RAD51* rs8017304 were not associated with PA invasiveness (Supplementary material).

Table VI. *TBX15 rs984222, DNM3 rs1011731, RAD51B rs8017304 and RAD51B rs2588809 genotype and allele frequencies in patients grouped by PA recurrence and healthy subjects.*

SNP	Genotype/ Allele	Frequency					
		PA without recurrence n (%) n=91	Control group n (%) n=283	*p*-Value	PA with recurrence n (%) n=22	Control group n (%) n=283	*p*-Value
TBX15	GG	49 (53.85)	141 (49.82)	0.786	15 (68.18)	141 (49.82)	0.252
rs984222	GC	36 (39.56)	120 (42.40)		6 (27.27)	120 (42.40)	
	CC	6 (6.59)	22 (7.78)		1 (4.55)	22 (7.78)	
	Allele						
	G	134 (73.63)	402 (71.02)	0.498	36 (81.82)	402 (71.02)	0.125
	C	48 (26.37)	164 (28.98)		8 (18.18)	164 28.98)	
DNM3	AA	28 (30.77)	90 (31.80)	0.929	6 (27.27)	90 (31.80)	0.900
rs1011731	AG	45 (49.45)	142 (50.18)		12 (54.55)	142 (50.18)	
	GG	18 (19.78)	51 (18.02)		4 (18.18)	51 (18.02)	
	Allele						
	A	101 (55.49)	322 (56.89)	0.741	24 (54.55)	322 (56.89)	0.762
	G	81 (44.51)	244 (43.11)		20 (45.45)	244 (43.11)	
RAD51	AA	41 (45.05)	130 (45.94)	0.941	8 (36.36)	130 (45.94)	0.203
rs8017304	AG	39 (42.86)	116 (40.99)		13 (59.09)	116 (40.99)	
	GG	11 (12.09)	37 (13.07)		1 (4.55)	37 (13.07)	
	Allele						
	A	121 (66.48)	376 (66.43)	0.989	29 (65.90)	376 (66.43)	0.943
	G	61 (33.52)	190 (33.57)		15 (34.09)	190 (33.57)	
RAD51B	CC	61 (67.03)	198 (69.96)	**0.005**	13 (59.09)	198 (69.96)	0.484
rs2588809	CT	16 (17.58)	70 (24.73)		8 (36.36)	70 (24.73)	
	TT	14 (15.39)	15 (5.31)		1 (4.55)	15 (5.31)	
	Allele						
	C	138 (75.82)	466 (82.33)	0.052	34 (77.27)	466 (82.33)	0.401
	T	44 (25.18)	100 (17.67)		10 (22.73)	100 (17.67)	

PA: Pituitary adenoma; *p*-Value: Bonferroni corrected level of significance, differences are considered statistically significant when $p<0.05/4$. Significant *p*-Values are shown in bold.

Discussion

Our study analyzed the *TBX15* rs984222, *DNM3* rs1011731, *RAD51B* rs8017304 and *RAD51B* rs2588809 gene polymorphisms in PA patients (*n*=113) and healthy control subjects (*n*=283). The results were compared by gender, age, and the clinical course of the disease. Studies of these polymorphisms analyzing PA association with rs984222, rs1011731, rs8017304, and rs2588809 have not been performed yet, to the best of our knowledge.

The role of TBX family genes (*TBX2* and *TBX3*) in oncogenic processes was associated with an increase of their expression level, as they have been found to be overexpressed in different types of cancer, including breast, cervical, ovarian, pancreatic, liver, and bladder cancer (58, 59). *TBX15* hypermethylation has been evaluated in prostate and ovarian carcinomas (19, 20). No studies have been performed in association with any brain tumors, including PA. Our study was the first to find that the C allele of *TBX15* rs984222 polymorphism reduced PA's recurrence (*p*=0.037).

Table VII. *RAD51B rs2588809 association with PA without recurrence.*

Model	Genotype	OR (95% CI)	*p*-Value	AIC
Co-dominant	C/T	0.747 (0.405; 1.378)	0.350	398.342
	T/T	7.842 (2.890; 21.277)	**<0.001**	
Dominant	C/T+T/T	1.293 (0.777; 2.150)	0.323	418.081
Recessive	T/T	8.394 (3.122; 22.571)	**<0.001**	397.245
Overdominant	C/T	0.637 (0.349; 1.164)	0.143	414.772
Additive	T	1.676 (0.114; 2.457)	**0.008**	410.252

OR: Odds ratio; AIC: Akaike information criterion; *p*-Value: Bonferroni corrected level of significance, differences are considered statistically significant when $p<0.05/4$. Significant *p*-Values are shown in bold.

DNM3 has been shown to be involved in various malignancies (28-37). Marino *et al.* have reported DNM3 expression in the brain and testicles and less often in the lungs and heart (29). Inokawa *et al.* and Shen *et al.* have found that DNM3 is hypermethylated in hepatocellular cancer (HCC) (33-34). Zhang *et al.* have also studied the

Table VIII. *TBX15 rs984222, DNM3 rs1011731, RAD51B rs8017304 and RAD51B rs2588809 genotype and allele frequencies in patients grouped by PA hormonal activity and healthy subjects.*

SNP	Genotype/ Allele	Frequency					
		Inactive PA group n=53 n (%)	Control group n=283 n (%)	*p*-Value	Active PA group n=60 n (%)	Control group n=283 n (%)	*p*-Value
TBX15	GG	30 (56.60)	141 (49.82)	0.636	35 (58.33)	141 (49.82)	0.252
rs984222	GC	20 (37.74)	120 (42.40)		22 (36.67)	120 (42.40)	
	CC	3 (5.6)	22 (7.78)		3 (5)	22 (7.78)	
	Allele						
	G	80 (75.47)	402 (71.02)	0.351	92 (76.67)	402 (71.02)	0.125
	C	26 (24.53)	164 (28.98)		28 (23.33)	164 (28.98)	
DNM3	AA	16 (30.19)	90 (31.81)	0.804	18 (30)	90 (31.81)	0.900
rs1011731	AG	29 (54.72)	142 (50.17)		28 (46.67)	142 (50.17)	
	GG	8 (15.09)	51 (18.02)		14 (23.33)	51 (18.02)	
	Allele						
	A	61 (57.55)	322 (56.89)		64 (53.33)	322 (56.89)	0.762
	G	45 (42.45)	244 (43.11)	0.900	56 (46.67)	244 (43.11)	
RAD51B	AA	24 (45.28)	130 (45.94)	0.996	25 (41.67)	130 (45.94)	0.358
rs8017304	AG	22 (41.51)	116 (40.99)		30 (50.0)	116 (40.99)	
	GG	7 (13.21)	37 (13.07)		5 (8.33)	37 (13.07)	
	Allele						
	A	55 (51.87)	376 (66.43)	**0.004**	80 (66.67)	376 (66.43)	0.960
	G	51 (48.13)	190 (33.57)		40 (33.33)	190 (33.57)	
RAD51B	CC	33 (62.26)	198 (69.96)	0.098	41 (68.33)	198 (69.96)	0.060
rs2588809	CT	13 (24.53)	70 (24.73)		11 (18.33)	70 (24.73)	
	TT	7 (13.21)	15 (5.31)		8 (13.34)	15 (5.31)	
	Allele						
	C	79 (74.53)	466 (82.33)	0.059	93 (77.5)	466 (82.33)	0.215
	T	27 (25.47)	100 (17.67)		27 (22.5)	100 (17.67)	

p-Value: Bonferroni corrected level of significance, differences are considered statistically significant when $p<0.05/4$. Significant *p*-Values are shown in bold.

Table IX. *RAD51B rs2588809 associations with PA hormonal activity.*

Model	Genotype	OR (95% CI)	*p*-Value	AIC	Model	Genotype	OR (95% CI)	*p*-Value	AIC
RAD51B rs2588809					*RAD51B* rs2588809				
Active PA					Inactive PA				
Co-dominant	C/T	0.678 (0.323; 1.421)	0.303	309.171	Co-dominant	C/T	1.122 (0.559; 2.249)	0.746	286.264
	T/T	6.508 (2.146; 19.734)	**0.001**			T/T	7.247 (2.293; 22.906)	**0.001**	
Dominant	C/T+T/T	1.126 (0.612; 2.074)	0.702	319.894	Dominant	C/T+T/T	1.593 (0.862; 2.942)	0.137	292.775
Recessive	T/T	7.103 (2.366; 21.320)	**<0.001**	308.292	Recessive	T/T	7.260 (2.260; 21.840)	**0.001**	284.368
Overdominant	C/T	0.597 (0.288; 1.239)	0.166	317.966	Overdominant	C/T	0.970 (0.491; 1.917)	0.931	294.917
Additive	T	1.513 (0.949; 2.414)	0.082	317.159	Additive	T	1.865 (1.154; 3.014)	**0.011**	288.799

OR: Odds ratio; AIC: Akaike information criterion; *p*-Value: Bonferroni corrected level of significance, differences are considered statistically significant when $p<0.05/4$. Significant *p*-Values are shown in bold.

mechanism of DNM3 in HCC (60). Teicher *et al*. have reported liposarcoma 1q24.3 amplifications involving DNM3 (29) while low DNM2 expression has been associated with tumor invasion and metastasis in cervix carcinoma and up-regulation of matrix metalloproteinase 2 (MMP-2) expression (61). The *DNM3* gene has also been investigated as a possible molecular marker for diagnosis and gene therapy of malignant diseases (38). Yang *et al*. have

Table X. *TBX15 rs984222, DNM3 rs1011731, RAD51B rs8017304 and RAD51B rs2588809 genotype and allele frequencies in patients grouped by PA invasiveness and healthy subjects.*

SNP	Genotype/ Allele	Frequency					
		Non-invasive PA group n=44 n (%)	Control group n=283 n (%)	*p*-Value	Invasive PA group n=69 n (%)	Control group n=283 n (%)	*p*-Value
TBX15	GG	26 (59.09)	141 (49.82)	0.300	39 (56.52)	141 (49.82)	0.600
rs984222	GC	17 (38.64)	120 (42.40)		25 (36.23)	120 (42.40)	
	CC	1 (2.27)	22 (7.78)		5 (7.25)	22 (7.78)	
	Allele						
	G	69 (78.41)	402 (71.02)	0.151	103 (74.64)	402 (71.02)	0.398
	C	19 (21.59)	164 (28.98)		35 (25.36)	164 (28.98)	
DNM3	AA	14 (31.82)	90 (31.81)	0.732	20 (28.99)	90 (31.81)	0.868
rs1011731	AG	20 (45.45)	142 (50.17)		37 (53.62)	142 (50.17)	
	GG	10 (27.73)	51 (18.02)		12 (17.39)	51 (18.02)	
	Allele						
	A	48 (54.55)	322 (56.89)	0.679	77 (55.79)	322 (56.89)	0.816
	G	40 (45.45)	244 (43.11)		61 (44.21)	244 (43.11)	
RAD51B	AA	15 (34.09)	130 (45.94)	0.232	34 (49.28)	130 (45.94)	0.773
rs8017304	AG	24 (54.55)	116 (40.99)		28 (40.58)	116 (40.99)	
	GG	5 (11.36)	37 (13.07)		7 (10.14)	37 (13.07)	
	Allele						
	A	54 (61.36)	376 (66.43)	0.351	96 (69.57)	376 (66.43)	0.482
	G	34 (38.64)	190 (33.57)		42 (30.43)	190 (33.57)	
RAD51B	CC	26 (59.09)	198 (69.96)	**0.008**	48 (69.47)	198 (69.96)	0.280
rs2588809	CT	10 (22.72)	70 (24.73)		14 (20.29)	70 (24.73)	
	TT	8 (18.19)	15 (5.31)		7 (10.14)	15 (5.31)	
	Allele						
	C	62 (70.45)	466 (82.33)	**0.008**	110 (79.71)	466 (82.33)	0.473
	T	26 (29.55)	100 (17.67)		28 (20.29)	100 (17.67)	

p-Value: Bonferroni corrected level of significance, differences are considered statistically significant when $p<0.05/4$. Significant *p*-Values are shown in bold.

Table XI. *RAD51B gene rs2588809 association with PA invasiveness.*

Model	Genotype	OR (95% CI)	*p*-Value	AIC	Model	Genotype	OR (95% CI)	*p*-Value	AIC
RAD51B rs2588809					*RAD51B* rs2588809				
Inactive PA					Non-invasive PA				
Co-dominant	C/T	0.755 (0.387; 1.473)	0.410	343.800	Co-dominant	C/T	1.095 (0.503; 2.382)	0.819	248.474
	T/T	4.881 (1.570; 15.172)	**0.006**			T/T	10.513 (3.381; 32.688)	**<0.001**	
Dominant	C/T+T/T	1.073 (0.600; 1.919)	0.813	350.311	Dominant	C/T+T/T	1.820 (0.945; 3.503)	0.073	257.197
Recessive	T/T	5.212 (1.693; 16.050)	**0.004**	342.503	Recessive	T/T	10.259 (3.368; 31.255)	**<0.001**	244.526
Overdominant	C/T	0.693 (0.358; 1.342)	0.277	349.125	Overdominant	C/T	0.878 (0.413; 1.868)	0.736	260.187
Additive	T	1.357 (0.857; 2.148)	0.193	348.735	Additive	T	2.222 (1.352; 3.652)	**0.002**	250.945

OR: Odds ratio; AIC: Akaike information criterion; *p*-Value: Bonferroni corrected level of significance, differences are considered statistically significant when $p<0.05/4$. Significant *p*-Values are shown in bold.

discussed the importance of the *DNM3* gene in gliomas. As the *DNM3* gene is the target of miR-221, the overexpression of *DNM3* could reverse its tumor-promoting effect (31-32). Based on these findings, we sought to examine whether a polymorphism in the *DNM3* promoter could impact PA development risk. Unfortunately, in our study, we did not find any statistically significant differences analyzing *DNM3* rs1011731 gene polymorphism in relation to PA.

Concerning theother two gene polymorphisms, we found that the *RAD51B* rs2588809 CC genotype and the rs8017304 AG genotype might increase the probability of PA recurrence and invasiveness. Also, we proved that the *RAD51B* rs2588809 TT genotype might increase the odds of PA development in women and may be associated with PA development without recurrence. The *RAD51B* gene has previously been studied in other tumor types (breast, ovarian, and lung cancers (32, 41) but not in brain tumors, so we could not compare our results with the results of other authors.

RAD51B has been previously evaluated as a candidate gene for breast cancer predisposition, but no mutation was detected in a study of 188 multiple-case breast cancer families (62). Previous studies have identified chromosomal rearrangements disrupting *RAD51B* in benign tumors, particularly uterine leiomyomas (42, 43). In addition, the findings by Golmard and colleagues must be interpreted in the context of two genome-wide association studies (GWAS), which identified the minor allele of single nucleotide polymorphisms in *RAD51B* acting as a low-risk factor for breast cancer: the rs999737 (63) and rs1314913 (64), located in *RAD51B* introns 10 and 7, respectively. Results by Mengyin *et al*. also suggest that *RAD51B* could be a candidate prognostic factor for non-small cell lung cancer patients (41).

Overall, the present study of the *TBX15* rs984222, *DNM3* rs1011731, *RAD51B* rs8017304, and *RAD51B* rs2588809 gene polymorphisms requires future replication in studies with higher sample sizes to confirm the association of *RAD51B* rs2588809 with PA.

Conclusion

The *RAD51B* rs2588809 TT genotype was more common in women with PA than in healthy women, and the T allele was less frequent in men with PA than in healthy men. The *RAD51B* rs2588809 T allele increased the potential for PA invasiveness and PA activity. The likelihood of PA recurrence was reduced by the TT genotype and each T allele.

Data Availability

The genotyping data used to support the findings of this study is available from the corresponding author upon request.

Supplementary Material

Available at: https://docs.google.com/document/d/1U5Za-8j3e9mbHEye0LJlEcwVPL1f7-uSt7HlwRpslqM/edit?usp=sharing.

Conflicts of Interest

None of the Authors has any proprietary interests or conflicts of interest related to this submission.

Authors' Contributions

Conceptualization, R.L., and B.G.; Data curation, A.V., G.G., and B.G.; Writing-Original draft preparation, I.L., G.J., and R.L; Methodology, A.V., G.G., B.G., L.K, and R.L.; Investigation, A.V., G.G., G.J., I.L., and L.K.; Validation, L.K., and R.L.; Supervision, R.L., and B.G.; Writing-Reviewing and Editing, R.L.

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