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Significant Association of Proline Allele in Tp53 Gene, Arg72pro Polymorphism in Brain Tumors and its Prognostic Value

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Abstract

Background: In TP53 gene, Arg72Pro polymorphism has been suggested to be associated with genetically determined susceptibility in various types of cancers including brain tumors. Our objective was to investigate the possible association between TP53 Arg72Pro polymorphism with brain tumor susceptibility and to examine its correlation with the clinico-pathologic variables of tumor cases for oncologic prognosis of patients.

Materials and methods: The TP53 Arg72Pro genotypes were determined by Polymerase Chain Reaction-Based Restriction Fragment Length Polymorphism (PCR-RFLP) analysis in 90 age and gender matched brain tumor cases and 130 healthy controls.

Results: We found significant difference in the frequency of Pro allele as 0.47 in cases versus 0.37 in controls ($p<0.05$).Though the distribution of the TP53, 72Pro genotypes in patients were higher (24.4%) compared with the control group (17.7%) with an odds ratio of 1.9 but no statistical difference was found ($p>0.05$). Proline related allele/genotype (GC) was significantly found associated in high grade malignant brain tumors, neuroepithelial tumors ($p<0.05$). Overall and disease-free survivals were calculated but no significant statistical difference was observed between the two groups ($p>0.05$).

Conclusion: Though overall distribution did not reveal significant association in TP53 Arg72Pro polymorphism among cases and controls but proline related genotype was found associated with susceptibility to the disease pathology.

Keywords: Brain tumor; Arg72Pro polymorphism; TP53; Polymorphism; Allele; Genotype; Kashmir

Introduction

Brain tumors in humans are the third most common cause of death among 18 to 35 year olds, and their incidence is increasing [1]. The incidence of primary malignant brain tumors has been increasing over the past 30 years, especially in elderly persons [2]. As per a hospital based study (2010: data unpublished) here in valley of Kashmir, nearly 2000 cases of brain tumors have been treated in which male: female ratio was reported as 1.47:1. The common age group found to be affected was 41-50 years of age. The most common brain tumor found in the valley of Kashmir is glioma which accounts for 51.3% of all the cases and among these glioblastoma multiforme is the commonest accounting for 49.5% of cases.

Predisposition to several human cancers has been associated with genetic polymorphisms, which may represent an important contribution to cancer susceptibility and tumor behavior. In the TP53 gene, several polymorphisms have been identified, both in non-coding and coding regions [3,4]. Most of these polymorphisms are single-nucleotide polymorphisms (SNP) affecting a single base. Within the coding regions of TP53, codon 72 (Arg72Pro) in exon 4 is a frequent functional SNP that leads to an arginine-proline amino acid change, which has been reported by many authors [5,6]. In human populations, codon 72 of TP53 has either the sequence CCC, which encodes proline, or CGC, which encodes arginine. The variants are hereafter abbreviated p53-P72 and p53-R72. Dumont et al. [6] reported that the Arg72 allele, if in homozygous, has an apoptosis inducing ability 15-fold higher compared to the Pro72 allele. According to Leu et al. [7], this high-apoptosis inducing ability of the Arg72 allele is partly due to its mitochondrial location, which makes it possible for TP53 to have a direct interaction with pro-apoptotic BAK protein. Studies on this SNP function were the basis for testing its impact on the risk and progression of tumors, where the less apoptotic allele Pro72 was associated with increased risk for development of tumors [8-10]. Arg72 of the TP53 SNP homozygote is considered to be a risk factor in the development of cancer [11]. In contrast, some investigators demonstrated the non-association between the different TP53 polymorphisms and individual cancer development [12]. Other studies revealed the higher risks with Pro72 in the TP53 SNP homozygote [4,13].

Few studies have addressed the association of Arg72Pro polymorphism with susceptibility to brain tumors and the results obtained are inconsistent. In the present investigation, a case-control

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study was conducted for the first from this region to examine the genotype distribution of TP53 Arg72Pro SNP and to search for an association between brain tumors and TP53 SNPs, using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) approach.

Material and Methods

This case-control study was conducted in the Department of Neurosurgery and Immunology and Molecular Medicine at Sheri-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, India. Blood samples were collected from 90 histologically proven brain tumors patients under the care of Neurosurgery Department. The patient group comprised of 41 males (45.5%) and 49 females (54.5%). Blood samples of 130 healthy individuals were taken as controls which comprised of 62 males (47.7%) and 68 females (52.3%). Mean age in patients was 40.7 years (range=7-70 years) and in control subjects was 39.8 years (range=8-67years). All cases and controls were of ethnic Kashmiri origin from different regions of Jammu and Kashmir. The study was approved by the Ethical Committee of the Institute (SKIMS).

DNA extraction

Genomic DNA was isolated both from patients and healthy controls using standard proteinase-K digestion, phenol/chloroform extraction, and ethanol precipitation method.

Polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP)

PCR was carried out in a final volume of 25 µL containing 50-250 ng genomic DNA template, 1x PCR buffer (Biotools, B & M Labs, Madrid, Spain) with 2 mmol/L $MgCl_2$, 50 µmol/L dNTPs (Biotools, B & M Labs), and 0.5 U *Taq polymerase* (Biotools, B & M Labs) using 0.4 µmol/L of each primer (Genscript, Piscataway, NJ)forward primer 5'-TCCCCCTTGCCGTCC CAA-3' and a reverse primer 5'-CGTGCAAGTCACAGACTT-3'. The cycling condition were 95°C for 5min of one cycle; followed by 94°C for 30 sec, 54°C for 30 sec and 72°C for 30sec for 30 cycles each and final elongation cycle of 72°C for 5min. The PCR products were visualized by 2% agarose electrophoresis to confirm the reaction.

For RFLP, the PCR products of TP53 Arg72Pro SNP were digested with *BstU* I (Fermentas, Inc., Glen Burnie, MD) (1U at 37°C for 16 hours). The Arg/Arg wild (GG) displayed two bands (160 and 119 bp); the Pro/Pro variant (CC) was identified by a single band (279 bp); and heterozygous Arg/Pro variant (GC) displayed three bands (279, 160, and 119 bp). For quality control, each PCR reaction used distilled water instead of DNA as a negative control, and more than 10% of the samples were analyzed twice. DNA fragments were subjected to electrophoresis on a 2-3% agarose gel for resolution. Great care was taken to minimize sources of bias and to avoid the overestimation of results.

Statistical analysis

Analysis of data was performed using the SPSS computer software (SPSS, Chicago, IL). Chi- square test was used to compare categorical variables. The odds ratio and its 95% confidence interval were used to determine the association between the brain tumor risk and the TP53 Arg72Pro polymorphism. Statistical significance was set at $p< 0.05$. A goodness-of-fit chi-square test was used to determine whether the polymorphisms were in Hardy-Weinberg equilibrium between cases and controls. Kaplan-Meier curves were constructed to assess overall survival and differences among groups were analyzed by the log-rank test.

Results

Our study was a hospital based case-control study comprising of 90 brain tumor patients which were frequency matched to age and gender with 130 healthy controls. No specific gender or age related differences were observed between the groups (p>0.05). The patients comprised of 27 smokers and 63 non-smokers. The control subjects comprised of 32 smokers and 98 non-smokers. No significant difference was seen in dwelling and smoking status (p>0.05). Only one patient had a positive family history of brain tumors. The most common co-morbidity in the patient group was hypertension (25.6%) followed by diabetes (2.2%) (Table 1).

Fifteen patients had anterior fossa (16.7%), fifty-four patients had middle fossa (60.0%) and twenty-one patients had posterior fossa tumors (23.3%). Out of the 90 patients, 53 had intra-axial and 37 were extra-axial tumors (Table 1). The clinic-pathological characteristics are detailed in Table 1.

The genotypic and allelic frequencies of TP53 Arg72Pro in both the patients and controls are shown in Table 2. The frequencies of the Arg/Arg, Arg/Pro, and Pro/Pro genotypes in the patient group were 31.1%, 44.4% and 24.4%, respectively compared to controls the frequencies of the Arg/Arg, Arg/Pro, and Pro/Pro genotypes were 43.1%, 39.2%, and 17.7%, respectively (p>0.05). Though the distribution of the TP53, 72Pro genotypes in patients was higher (24.4%) compared with the control group (17.7%) with an odds ratio of 1.9 but no statistical difference was found (Table 2). On the other hand, we found significant difference in the frequency of Pro allele as 0.47 in cases versus 0.37 in controls (p<0.05). The frequency of distribution of the Pro variant (Pro/Pro+Pro/Arg) was marginally abundant in cases as against controls (68.9% v/s 56.9%) with an OR of 1.7 (p>0.05) (Table 2). Further, female group had a significant association with proline related allele/genotype in brain tumor cases as compared to controls with Proline genotypic frequency of 34.6% in case versus 22.0% in controls (p<0.05). Per copy allelic frequency of proline in cases was also found significant in females with frequency 0.57 in cases versus 0.37 in controls (p<0.05) (Table 3).

When further stratified into various pathological variables, our study found higher frequency of Proline related allele/genotype (GC) in high grade brain tumors as compared to lower grade tumors (p>0.05; Table 3). Similarly, frequency of Proline was found to dominate in the malignant group of brain tumors (37.2 and 57%) compared to arginine (23.3% and 43.7%). Moreover, the present study showed a significant difference in the distribution of proline related allele/genotype in Neuroepithelial tumors (p>0.05) in comparison to Meningeal type (Table 3).

Kaplan-Meier survival analysis was performed to evaluate any possible association between TP53 Arg72Pro polymorphism and overall survival of patients. The mean follow-up period was 9.3 months (range 0-21 months). No statistically significant difference was observed (P> 0.05) (Figure 1). We also compared the overall survival between the Pro/Pro + Arg/Pro genotype frequencies and Arg/Arg genotype and found no significant differences were observed (P>0.05) (Figure 2).

Discussion

Tumor suppressor gene, Tp53, is implicated in a wide range of human cancers, including brain tumors. Genetic polymorphisms are known to play a role on cancer susceptibility, and their role in brain tumors is starting to be evaluated. Several polymorphisms have been associated with brain tumor susceptibility [14-16]. Among the functional

Characteristic		Patients		Control		p value
		n	%	n	%	
Age (yr)	≤ 10	3	3.3	6	4.6	0.932
	11 to 20	13	14.4	11	8.5	
	21 to 30	8	8.9	18	13.8	
	31 to 40	23	25.6	31	23.8	
	41 to 50	17	18.9	28	21.5	
	51 to 60	17	18.9	24	18.5	
	> 60	9	10.0	12	9.2	
	mean ± SD	40.7 ± 16.9 (7, 70)		39.8 ± 15.6 (8, 67)		
Gender	Male	41	45.6	62	47.7	0.755
	Female	49	54.4	68	52.3	
Dwelling	Rural	67	74.4	96	73.8	0.921
	Urban	23	25.6	34	26.2	
Smoker	Yes	27	30.0	32	24.6	0.377
	No	63	70.0	98	75.4	
Histopathology	Neuroepithelial Tissue Tumor	35	38.9			
	Meningeal Tumor	27	30.0			
	CNS Lymphoma	4	4.4			
	Tumors of Sellar Region	6	6.7			
	Metastatic Tumor	2	2.2			
	Others	2	2.2			
	Cranial Nerve Tumor	14	15.6			
Tumor Type	Benign	47	52.2			
	Malignant	43	47.8			
Tumor Grade	Low	33	47.1			
	High	37	52.9			
Vascularity	Less Vascular	40	44.4			
	Moderately Vascular	26	28.9			
	Highly Vascular	24	26.7			

[a]Pro/Pro+ Pro/Arg genotype frequencies vs. Arg/Arg genotype.

Table 1: Distribution analysis of selected demographic and risk factors in brain tumor cases and controls.

Genotype	Patients(n=90) n %		Controls(n=130) n%		*p*-value	OR	95% CI
Pro/Pro	22	24.4	23	17.7	0.084	1.9	0.92-3.99
Arg/Pro	40	44.4	51	39.2	0.150	1.6	0.85-2.89
Arg/Arg	28	31.1	56	43.1	Reference	-	-
Pro/Pro+Pro/Arg [a]	62	68.9	74	56.9	0.072	1.7	0.95-2.94
Pro allele	84	46.7	97	37.3	0.049	1.5	1.00-2.16
Arg allele	96	53.3	163	62.7	Reference	-	-

Table 2: Allele and Genotype frequencies in patients and controls.

Parameter	Genotype/Allele	Study n%		Control n%		p- value	OR	95% CI
Male	Pro/Pro	05	14.6	08	12.9	0.7	1.2	0.5-3.0
	Arg/Pro	18	43.9	18	29.0	.12	2.0	1.7-6.0
	Arg/Arg	18	41.4	36	58.0	Reference		
	Pro/Pro +Pro/Arg [a]	24	58.5	26	41.9	0.1	0.6	0.3-2.6
	Pro allele	30	36.5	34	27.8	0.1	1.5	1.1-4.0
	Arg allele	52	63.5	90	73.7	Reference		
Female	Pro/Pro	17	34.6	14	22.0	**0.04**	2.5	1.1-4.4
	Arg/Pro	22	44.8	33	48.5	0.4	0.6	0.3-2.8
	Arg/Arg	10	20.4	21	29.4	Reference		
	Pro/Pro +Pro/Arg [a]	39	79.5	47	69.1	0.2	0.6	0.4-2.9
	Pro allele	56	57.1	51	37.5	**0.01**	1.9	1.3-3.0
	Arg allele	42	48.8	75	55.1	Reference		
Low Grade Tumor	Pro/Pro	09	16.9	23	17.7	0.764	1.15	0.46-.88
	Arg/Pro	25	47.2	51	39.2	0.307	1.44	0.71.-91
	Arg/Arg	19	35.8	56	43.1	Reference	-	
	Pro/Pro +Pro/Arg [a]	34	64.2	74	56.9	0.367	1.35	0.69-2.61
	Pro allele	43	40.6	97	42.2	0.516	1.15	0.72-0.82
	Arg allele	63	59.4	163	57.8	Reference	-	-

High Grade Tumor	Pro/Pro	13	35.1	23	17.7	**0.009**	3.51	1.34-9.19
	Arg/Pro	15	40.5	51	39.2	0.189	1.83	0.75-4.45
	Arg/Arg	9	24.3	56	43.1	Reference	-	-
	Pro/Pro +Pro/Arg [a]	28	75.7	74	56.9	**0.039**	2.35	1.03-5.36
	Pro allele	41	55.4	97	42.2	**0.005**	2.09	1.23-3.52
	Arg allele	33	44.6	163	57.8	Ref.	-	-
Neuroepithelial Tissue Tumor	Pro/Pro	13	37.1	23	17.7	0.009	3.52	1.349.2
	Arg/Pro	13	37.1	51	39.2	0.329	1.58	0.643.94
	Arg/Arg	9	25.7	56	43.1	Reference	-	-
	Pro/Pro +Pro/Arg[a]	26	74.2	74	56.9	0.062	2.19	0.954.95
	Pro allele	39	55.7	97	42.2	0.005	2.11	1.233.59
	Arg allele	31	44.3	163	57.8	Reference	-	-
Meningeal Tumor	Pro/Pro	2	7.4	23	17.7	0.249	0.41	0.10-1.77
	Arg/Pro	13	48.1	51	39.2	0.696	1.19	0.50-2.80
	Arg/Arg	12	44.4	56	43.1	Reference	-	-
	Pro/Pro +Pro/Arg[a]	15	55.5	74	56.9	0.896	0.95	0.41-2.14
	Pro allele	17	31.5	97	42.2	0.418	0.77	0.41-1.44
	Arg allele	37	68.5	163	57.8	Reference	-	-
Malignant Tumor	Pro/Pro	16	37.2	23	17.7	**0.003**	3.89	1.56-9.71
	Arg/Pro	17	39.5	51	39.2	0.155	1.86	0.79-4.38
	Arg/Arg	10	23.3	56	43.1	Ref.		
	Pro/Pro +Pro/Arg[a]	33	76.7	74	56.9	**0.020**	2.50	1.14-5.47
	Pro allele	49	57.0	97	42.2	**0.001**	2.23	1.34
	Arg allele	37	43.0	163	57.8	Reference		
Benign Tumor	Pro/Pro	6	12.7	23	17.7	0.695	0.81	0.29-3.67
	Arg/Pro	23	48.9	51	39.2	0.358	1.40	0.68
	Arg/Arg	18	38.3	56	43.1	Reference		
	Pro/Pro +Pro/Arg[a]	29	61.7	74	56.9	0.569	1.22	0.612.25
	Pro allele	35	37.2	97	42.2	0.990	0.99	0.61-2.87
	Arg allele	59	62.7	163	57.8	Reference		

Table 3: Association between TP53 codon 72 genotypes and clinico-pathologic characteristics.

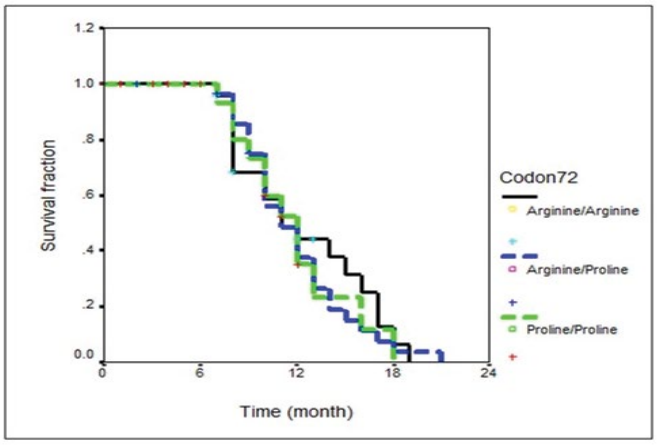

Figure 1: Overall survival in patients according to TP52Arg72Pro SNP.

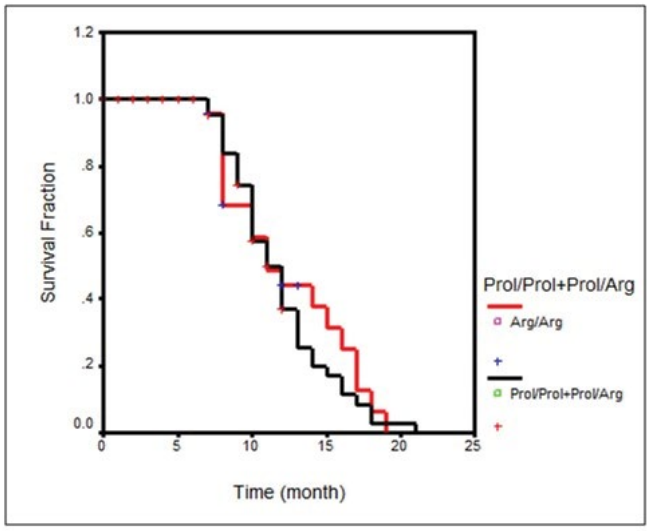

Figure 2: Kaplan Meier survival curves of brain tumor patients as a function of TP53 codon 72Pro genotype and codon 72Arg genotypes.

polymorphisms, codon 72 polymorphism of the TP53 gene contributes to the differences between individuals or races in susceptibility and severity of disease [17,18]. Though few studies have been conducted on brain tumors [19-21] to confirm the high risk of developing cancer with Arg72Pro polymorphism in TP53 gene, but these investigations indicated discrepancies with regard to the polymorphism.

In the present report conducted for the first time in Kashmir (North India), we evaluated the role of TP53 Arg72Pro polymorphism as a risk of susceptibility for developing brain tumor. Though our data showed no significant difference in the genotypic frequencies between brain tumor patients and controls but per copy of proline allele had significant differences in both the groups with frequency of proline allele as 0.47 in cases as against 0.37 in controls ($p<0.05$). Interestingly when cases were further stratified as cohort we found this Proline related allele to have an impact in the disease pathology. The findings

observed in the frequency of genotypes in our report are in agreement with those Lima-Ramos et al., Pinto et al., Uno et al. and Wang et al. [22-25] who reported no significant association of gliomas with TP53 Arg72Pro polymorphism. Similar results were seen by Biros et al., [2] that showed that the p53 *BstUI* polymorphism is not associated with increased risk of brain tumors. Likewise, Idbaih et al. [26] who found no association between oligodendroglial tumors and the SNP in codon 72 of TP53. Similarly Malmer et al. [27] partially complies with our report who investigated if polymorphisms of Tp53 were associated with an increased risk of meningioma and glioma and found no association with the SNP. At variance with these results, Parhar et al. [28] reported that the genotype distributions of the TP53 Arg72Pro between all brain tumors and controls were statistically significant (P<0.001) as well as their variant allele frequencies between cases and controls (P<0.001) This report is in partial agreement with our study in relation to significance of brain tumor cases with proline allele.

Our study is in agreement with Almeida et al. [1] who analyzed polymorphisms and DNA methylation of gene TP53 associated with extra-axial brain tumors and found significant association with Pro of the TP53 Arg72Pro polymorphism with increased risk of tumor development.

Interestingly when stratified by pathological events, our study found higher frequency of Proline related allele/genotype (GC) with significant difference in high grade brain tumors as compared to lower grade tumors (p>0.05). This is in conformity with the literature review of the available data by Minghain et al. [29] where results suggest that TP53 codon 72 C carriers (Pro) are associated with an increased risk of high-grade glioma in Europeans.

Similarly, in this study frequency of Proline was found to have a significant abundance in the malignant group of brain tumors. This pattern of scenario is hardly found in any of the studies conducted so far worldwide in any histological type of brain tumors. In stark contrast to our report, Lima-Ramos et al. [22] investigated different pathological parameters of the codon 72 of TP53 but results were insignificant.

Further, an association between the various histological subtypes of brain tumors and the Arg72Pro polymorphism was determined and a significant association was found between the neuroepithelial tissue tumors and the Pro/Pro genotype (p=0.009) and the Pro allele (p=0.005). These findings presented in this study are in agreement with those of Parhar et al. [28] and Zawlik et al. [30] as has been mentioned earlier. Both of them found a significant association between codon 72 polymorphism and the risk of gliomas.

There is a discrepancy about the role of TP53 Arg72Pro SNP in cancer patient prognosis. Few of the studies have revealed TP53 Arg72Pro SNP having a non-significant effect on oncologic prognosis for patients with many cancers [31,32], but other studies have shown this association for patients with breast and lung tumors [10,33]. Kaplan-Meier curves were performed to evaluate the possible association between the Arg72Pro polymorphism and overall patient survival. The mean follow-up period was 9.3 months (range 0-21 months). No significant difference was observed for the brain tumor patients and overall survival with any of the genotypes (P>0.05). These results are in agreement with those of Pinto et al., Almeida et al. and Lima-Ramoset al. [1,22,23]. In contrast, Zawlik et al. [30] revealed that TP53 codon 72 Pro allele was significantly associated with shorter survival among patients with glioblastomas carrying a TP53 mutation, and among those treated with surgery plus radiotherapy.

In conclusion proline allele was found associated significantly among cases and controls in addition with the disease pathology but the overall genotypic distribution did not reveal significant association in TP53 Arg72Pro polymorphism. Further studies on larger populations from other parts of the world may be more informative for delineating the association of Tp53 codon 72 polymorphism with brain tumors.

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