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Original Research

The Relationship Between Odontogenic Cyst and P53 Codon 72 And P53 Codon 175 Variants in Turkish Patients

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ABSTRACT

Objective: Odontogenic cysts that cause bone destruction can exhibit various types of metaplasia. Inherited genetic variants in codons 72 and 175, the hotspot codons of p53, known as the guardian of the genome, can cause a wide variety of cancers. We aimed to investigate the effects of the p53 codon 72 and p53 codon 175 variants on odontogenic cyst formation.

Methods: This research encompassed 71 individuals with odontogenic cysts and 90 without any conditions as a control group. After DNA was extracting, the p53 codon 72 was detected using PCR techniques, while p53 codon 175 was identified through allele-specific amplification-PCR.

Results: The presence of the p53 codon 72 GG genotype and its G allele was less frequent in the group with odontogenic cysts compared to the healthy participants. Conversely, the C allele was found more often in the cyst-afflicted group. For the p53 codon 175, the AA genotype and A allele were more common in the affected group, while the G allele was more predominant in the control group.

Conclusion: The p53 codon 175 AA genotype and A allele, p53 codon 72 C allele, and p53 codon 72/codon 175 CCAA combined genotype may be associated with odontagenic cyst formation. Individuals with this allele and genotype can be considered at risk for odontagenic cyst formation.

Keywords: Odontogenic cysts; Gene; Metaplasia

INTRODUCTION

Odontogenic cysts, which develop within the regions of the mandible and maxilla that bare teeth, are pathological cavities lined with epithelium and encased in fibrous connective tissue derived from odontogenic tissue. These cysts, which are capable of causing bone deterioration, can lead to resorption or displacement of neighboring teeth. Such cysts can be of either inflammatory or developmental origin [1]. It is widely recognized that odontogenic cysts, whether inflammatory or developmental, contain linings of squamous epithelial cells. These linings may undergo various forms of metaplasia, transforming from stratified squamous cells to highly differentiated ciliated columnar or mucous cells [2].

The role of p53, which is the most frequently mutated gene across diverse cancer types, has evolved since it was discovered four decades ago. Initially believed to be an oncogene, p53 was subsequently identified as an essential tumor suppressor [3]. P53 stringently controls cellular growth, induces apoptosis, and facilitates DNA repair under stress conditions. Mutations in p53

can disrupt these functions, contributing to tumor advancement and unchecked cellular proliferation. Mutations in p53 have been shown to cause protein aggregation, thereby inhibiting its function [4].

Two polymorphic variants arise because of an amino acid residue shift from arginine to proline at the 72nd codon of the p53 protein, each exhibiting distinct biological and biochemical attributes. The proline variant of p53 acts as a more robust activator of transcription factors but exhibits less potent apoptotic properties than the arginine variant, which is more prone to degradation [5]. This polymorphism at p53's 72nd codon is posited to play a crucial role in cancer development and pathogenesis [6]. However, a recent study suggested that this polymorphism selectively modulates functional metabolic pathways without influencing cell fate pathways, such as apoptosis and growth arrest under genotoxic stress [7].

Mutations in p53 are prevalent in solid tumors, with missense mutations being particularly common at codons 273, 248, and 175, which are known hotspots for mutations [8]. Among these, codon 175 is situated in the DNA-binding domain of p53 and is associated with global denaturation of the protein [9].

There is no original study in the literature on the effect of the variants observed in the p53 codon 72 and p53 codon 175 gene regions on odontogenic cyst development in the Turkish population. In the light of this information, this study aimed to investigate the effects of p53 codon 72 and p53 codon 175 variants on odontogenic cyst development in the Turkish population. The frequencies of the alleles and genotypes of p53 codons 72 and p53 codon 175 in individuals with odontogenic cysts were compared with those in healthy individuals. Additionally, the association between the demographic and clinical data of the participants and the distribution of genotypes was examined.

Main Points;

- The AA genotype and A allele frequency in the p53 codon 175 variant was high in individuals with odontogenic cysts.
- The C allele frequency in the p53 codon 72 variant was high in individuals with odontogenic cysts.
- The p53 codon 72/codon 175 CCAA combined genotype may be associated with odontagenic cyst formation.
- The p53 codon 72/codon 175 CCAA combined genotype can be considered to be at risk for odontogenic cyst formation.

MATERIALS AND METHODS

Study Design

This study is a single-center case-control study. All procedures conducted during the study strictly adhered to the ethical guidelines outlined in the Declaration of Helsinki. For the purpose of this study, the patient group consisted of 71 individuals diagnosed with odontogenic cysts, who sought treatment at the Oral and Dental Surgery outpatient clinic. In addition, a control group comprising of 90 healthy individuals was established. The participants provided 2 ml of venous blood collected in tubes pre-filled with ethylenediaminetetraacetic acid. DNA was subsequently extracted from these samples using the QIAamp DNA Extraction Kit (Qiagen, Valencia, California, United States).

Genotyping

Primers used to identify rs1042522 (p53 codon 72) in the Arg72 variant (5′- TCCCCCTTGCCGTCCCAA-3′; 5′-CTG GTGCAGGGGCCACGC-3′) and Pro72 variant (5′- GCCAGAGGC TGCTCCCCC-3′; 5′-CGTGCAAGTCACAGACTT-3). Genomic DNA (100ng) was amplified by polymerase chain reaction (PCR). A final volume of 25 µL was used for the PCR. The following protocol was used for the PCR amplification on a Thermo Cycler thermal cycler: 4 min at 95°C, 35 s at 94°C, 35 s at 60°C, 50 s at 72°C for the Pro72 variant and 4 min at 95 °C, 40 s at 94 °C, 40 s at 58 °C, 50 s at 72 °C for the the Arg72 variant, and for 35 cycles, with an extra min at 72 °C after the last cycle. The amplified products were visualized on a 3 % agarose gel. T100 Thermal Cycler (Bio-Rad Laboratories - Dubai Branch) device was used for this procedure.

We employed allele-specific amplification (ASA)-PCR to test for codon 175 (CGCCAC) variants in the p53 gene. This technique entails the amplification of particular alleles or DNA sequence variations at the same locus. Designing one or both PCR primers so that they partially overlap the location of sequence differences between the generated alleles is how specificity in ASA-PCR examination is achieved. Three primers were used for amplification. The third was created particularly for the mutant gene, whereas the other two were used to amplify the

wild-type allele. The primer sequences were as follows: the 3' end of the primer 1:5'-GCAGCGCTCATGGTGGGGGCAGT-3' contained a T residue. The 3' end of the primer, 2:5'-GCGCTCATGGTGGGGGCAGC-3, 'has a C residue. Unspecific primer 3:5'- TTGATTCCACACCCGCCCG. T100 Thermal Cycler (Bio-Rad Laboratories - Dubai Branch) device was used for this procedure.

Each sample under investigation underwent two PCR amplifications, one of which amplified the wild type (with primers 2 and 3), while the other amplified the p53 codon 175-point mutation using primers 1 and 3, yielding a 105 bp fragment. We detected two bands for heterozygotes and one band for homozygotes of the wild type in the electrophoretic pattern.

100 ng of genomic DNA, 1 unit of Taq polymerase (Thermo Fisher Scientific Inc., Porto Salvo), 0.1 mM oligonucleotide primers, 100 mM dNTPs, and 1.5 mM MgCl2 made up the PCR mixture. Both the mutant alleles and the wild type underwent the same thermal cycle protocols, which included denaturation at 94°C for 40 seconds, annealing at 66°C for 40 seconds, extension at 72°C for 40 seconds, and amplification for 30 cycles. Polymerase chain reaction (PCR) was performed using a Thermo Thermocycler. Template DNA was changed using PCR-grade water as a negative control. The amplified products were visualized on a 3% agarose gel.

Data Evaluation

We utilized the IBM's SPSS 22.0 22 for Windows (IBM, New York, USA) software for our statistical evaluations. For categorical information, we presented results in terms of percentage frequencies. For continuous information, results were given as the average plus or minus the standard deviation. To compare groups, we employed the chi-square test for categorical data and the independent t-test for continuous data.

RESULTS

This research evaluated 71 participants, with ages ranging from 14 to 72 years, who had confirmed diagnoses of odontogenic cysts. In contrast, the control group incorporated 90 healthy individuals, aged between 19 and 70 years. The mean age for those with odontogenic cysts stood at 35.99±14.08 years, while the average for the control group was 34.84±12.31 years. Among the cyst-diagnosed participants, 39 (54.93%) were female, and 32 (45.07%) were male. The control set consisted of 39 females (43.33%) and 51 males (56.67%). There was no significant difference between the control group and the participants with odontogenic cysts in terms of mean age and gender ratio.

The distribution frequencies for the genotypes and alleles of p53 codon 72 and p53 codon 175 variants across both sets of participants presented in Table 1.

For the genotype distribution related to p53 codon 72, a reduced frequency of the GG genotype was noted among the cyst-afflicted group compared to the controls, as detailed in Table 1.

Considering the allele distribution for p53 codon 72, those diagnosed with cysts showed a diminished presence of the G allele and an elevated presence of the C allele relative to the control group, as depicted in Table 1.

When assessing the genotype distribution associated with p53 codon 175, there was an evident increase in the frequency of the AA genotype among the patient group compared to the control participants, as illustrated in Table 1.

Regarding the allele distribution of p53 codon 175, the patient group demonstrated a decreased prevalence of the G allele and an augmented prevalence of the A allele in contrast to the controls, as outlined in Table 1.

A detailed examination was conducted on the combined genotype frequencies for the variants of p53 codons 72 and 175 across both sets of participants, and these findings are presented in Table 2.

From this combined assessment, the GGGA genotype appeared less frequently in the cyst-diagnosed group, while the CCAA genotype's frequency was more predominant among them, as shown in Table 2.

Participants' age, gender, cyst diagnostic features, cyst sizes were analyzed according to different genotypes of p53 codons 72 and 175. These detailed results are provided in Table 3.

After comprehensive evaluation, no direct association was found between the genotype distributions of the p53 codon 72 and p53 codon 175 variants and the factors like participant age, gender, cyst diagnosis details, cyst measurements, and locations, as specified in Table 3 ($p>0.05$).

Table 1. Genotype and allele distribution of p53 codon 72 and p53 codon 175 variants of the groups

Gene region Genotype/Allele	Patient n=71(%)	Control n=90 (%)	p*	OR (CI 95%)
p53 codon 72	**Genotype**			
GG	18 (25.35)	40 (44.44)	**0.012**	2.356 (1.197-4.637)
GC	29 (40.85)	31 (34.44)	>0.05	0.761 (0.400-1.447)
CC	24 (33.80)	19 (21.11)	>0.05	0.524 (0.259-1.061)
p53 codon 72	**Allele**			
G	65 (45.77)	111 (61.67)	**0.004**	0.525 (0.336-0.820)
C	77 (54.23)	69 (38.33)		
Gene region Genotype/Allele	**Patient n=71(%)**	**Control n=90 (%)**	**p**	**OR (CI 95%)**
p53 codon 175	**Genotype**			
GG	24 (33.80)	35 (38.89)	>0.05	1.246 (0.651-2.385)
GA	20 (28.17)	37 (41.11)	>0.05	1.780 (0.914-3.465)
AA	27 (38.03)	18 (20.00)	**0.011**	0.407 (0.201-0.824)
p53 codon 175	**Allele**			
G	68 (47.89)	107 (59.44)	**0.039**	0.627 (0.402-0.977)
A	74 (52.11)	73 (40.56)		

* Chi-square test

Table 2. Combined genotype distribution of p53 codon 72 and p53 codon 175 variants of the groups

Combined Genotype p53 codon 72/p53 codon 175	Patient n=71 (%)	Control n=90 (%)	p*
GGGG	7 (09.86)	14 (15.56)	>0.05
GGGA	6 (08.45)	19 (21.11)	**0.028**
GGAA	5 (07.04)	7 (07.78)	>0.05
GCGG	10 (14.08)	12 (13.33)	>0.05
GCGA	8 (11.27)	11 (12.22)	>0.05
GCAA	11 (15.49)	8 (08.89)	>0.05
CCGG	7 (09.86)	9 (10.00)	>0.05
CCGA	6 (08.45)	7 (07.78)	>0.05
CCAA	11 (15.49)	3 (03.33)	**0.007**

* Chi-square test

Table 3. The relationship between descriptive and clinical information of the patient group and genotype distribution of p53 codon 72 and p53 codon 175 variants

p53 codon 72					
Parameter		**GG n=18 (%)**	**GC n=29 (%)**	**CC n=24 (%)**	**p***
Gender n(%)	Male	7 (38.89)	13 (44.83)	12 (50.00)	>0.05
	Woman	11 (61.11)	16 (55.17)	12 (50.00)	
Age X±SD		38.28±12.84	37.10±13.86	32.92±5.25	>0.05
Diagnosis n(%)	Radicular cyst	17 (94.44)	20 (68.97)	21 (87.50)	>0.05
	Dentigerous cyst	1 (05.56)	3 (10.34)	2 (08.33)	
	Odontogenic keratocystic cyst	0 (00.00)	6 (20.69)	1 (04.17)	
Region n (%)	Maxilla Anterior	5 (27.78)	6 (20.69)	6 (25.00)	>0.05
	Maxilla Posterior	3 (16.67)	2 (06.90)	2 (08.33)	
	MandibulaAnterior	1 (05.56)	8 (27.59)	5 (20.83)	
	Mandibula Posterior	9 (50.00)	13 (44.83)	11 (45.83)	
Dimension (mm^2) X±SD		20.94±18.72	40.55±38.41	26.58±40.69	>0.05
p53 codon 175					
Parameter		**GG n=24(%)**	**GA n=20(%)**	**AA n=27(%)**	**p***
Gender n(%)	Male	8 (33.33)	11 (55.00)	13 (48.15)	>0.05
	Woman	16 (66.67)	9 (45.00)	14 (51.85)	
Age X±SD		32.33±13.21	34.75±14.60	40.15±13.88	>0.05
Diagnosis n(%)	Radicular cyst	22 (91.67)	17 (85.00)	19 (70.37)	>0.05
	Dentigerous cyst	1 (04.17)	1 (05.00)	4 (14.81)	
	Odontogenic cyst	1 (04.17)	2 (10.00)	4 (14.81)	
Cyst location n (%)	Maxilla Anterior	7 (29.17)	2 (10.00)	8 (29.63)	>0.05
	Maxilla Posterior	1(04.17)	2 (10.00)	4 (14.81)	
	MandibulaAnterior	1 (04.17)	6 (30.00)	7 (25.93)	
	Mandibula Posterior	15 (62.50)	10 (50.00)	8 (29.63)	
Cyst size (mm^2) X±SD		23.04±20.59	23.85±29.78	43.00±46.92	>0.05

* Chi-square test for categorical data and the independent t-test for continuous data

DISCUSSION

The P53 protein, renowned as a tumor suppressor, plays an indispensable role in deterring malignant transformations and is colloquially labeled as the genome's sentinel. An intriguing observation is that mutations in the P53 gene manifest in almost 50% of all human tumor cases. In the instances where such mutations are absent, the P53 regulatory network tends to be incapacitated. Most mutations linked to P53 are of the missense type, with a staggering 90% affecting specific codons, denoted as "hotspot codons", predominantly located in the DNA-binding region. Among the p53 gene's significant hotspot codons, codons 248, 245, and 175 are found within the DNA-binding domain, while codon 72 is positioned externally [10]. Genetic alterations within these specific codons seem to have a more profound impact on the susceptibility to various cancers than mutations in alternative genetic routes. Interestingly, the genetic features of cancer-associated variations within the P53 pathway share considerable similarities with the attributes of widely researched mutations in the same pathway [11].

Among the different polymorphisms within the p53 gene, the p53 codon 72 variant has garnered substantial scientific attention. This specific variant triggers a morphological change in the protein and is strategically located within the proline-rich domain, a segment instrumental in p53's apoptotic functionality [12]. A substantial study encompassing 27,958 individuals hinted that

the p53 codon 72 polymorphisms might have a subtle influence on predisposition to lung cancer, particularly accentuated in adenocarcinoma patients and those who have never smoked [13]. A separate comparative analysis between Asian and Caucasian females deduced that individuals with the GG genotype associated with p53 codon 72 polymorphisms generally had tumors of smaller dimensions compared to their counterparts with the CC genotype [14]. Delving into a broad literature review that amalgamated findings from 11 distinct case-control studies and an additional 10 standalone publications, there emerged a proposition that the p53 codon 72 variants might impart a protective shield against the development of glioblastoma [15].
A comprehensive review encompassing 13 studies with a total of 2,413 cases and 3,201 controls highlighted that the p53 codon 72 variants, in conjunction with Human Papilloma Virus infections, can collectively modify an individual's predisposition to oral cancer. Additionally, the p53 codon 72 variants may play a role in the progression and onset of oral cancer. However, the association between susceptibility to oral cancer and the p53 codon 72 variant appears to be subject to variation among diverse ethnic populations [16]. Research conducted on Taiwanese subjects revealed that individuals possessing the Arg/Arg (GG genotype) at p53 codon 72 were at a risk 2.68 times greater risk of oral cancer than those possessing the CC genotype (Pro/Pro) [17]. Conversely, a study involving Iranian subjects determined that the CC genotype (Pro/Pro) was a contributing risk factor for oral squamous cell carcinoma, particularly in the anatomical location of the tumor and in individuals below 50 years [18]. Additionally, another investigation of Taiwanese participants indicated that p53 codon 72 Pro homozygosity (CC genotype) was associated with an elevated likelihood of hypopharyngeal tumor development [19].

In the present study involving Turkish participants, the ratio of patients with odontogenic cysts carrying the GG genotype in the p53 codon 72 variant was found to be less than the ratio observed in their healthy counterparts. Moreover, the occurrence of the G allele was diminished in patients with odontogenic cysts compared to the healthy population, while the frequency of the C allele was higher in the patient group.

An investigation in a Thai cohort revealed that the CC genotype of the P53 gene codon 72 increased the probability of developing sporadic keratocystic odontogenic tumors [20]. In contrast, another study in the same Thai demographic determined that the GG genotype of the P53 gene codon 72 could play a crucial role in the genesis of ameloblastoma, suggesting that the heightened risk associated with the P53 codon 72 GG genotype may remain independent of the tumors' clinical characteristics [21].

Participants were categorized into three distinct diagnostic groups: radicular cysts, dentigerous cysts, and odontogenic keratocystic cysts. No associations were observed between the frequencies of the GG, GC, and CC genotypes of the p53 codon 72 variant and factors such as patient age, sex, type of cyst, cyst dimensions, and cyst location among these individuals.

Over 8000 mutations in p53 have been documented. The diversity of these mutations is subject to variation across different tumor types, with more than half concentrated in three predominant codons:175, 248, and 273. The polymorphism observed in codon 175, which is among the key codons, may potentially serve as an indicator of the progression of colorectal cancer. Furthermore, it could prove beneficial in evaluating the confines of surgical excision [22]. Mutations of p53 in glioblastoma multiforme, the most prevalent primary brain tumor, are commonly found within the DNA-binding domain, indicating that the region encompassing p53 codon 175 is a mutation hotspot. These alterations often lead to a variety of effects, including gain of function, loss of function, and dominant negative mutations in p53 [23].

No existing studies have investigated p53 codon 175 variants in individuals presenting with oral symptoms. This study, pioneering in its nature, discovered that the proportion of patients diagnosed with odontogenic cysts possessing the AA genotype in the p53 codon 175 polymorphism surpassed that of healthy individuals with the same genotype. Additionally, the prevalence of the A allele was elevated in individuals with odontogenic cysts compared to healthy subjects, while the frequency of the G allele was diminished in patients with odontogenic cysts relative to the healthy population. Moreover, no associations were identified between the frequencies of the GG, GA, and AA genotypes of the p53 codon 175 variant and variables such as patient age, sex, cyst classification, cyst dimensions, and cyst location among these participants.

Our study is a single-center study conducted with Turkish patients. This can be considered as a limitation of our study. On the other hand, it can also be considered as a reference study for future multicenter studies.

CONCLUSIONS

In conclusion, individuals diagnosed with odontogenic cysts exhibited a decreased prevalence of the GG genotype for the p53 codon 72 variant and an increased prevalence of the AA genotype for the p53 codon 175 variant compared to their healthy counterparts. Additionally, the C allele for p53 codon 72 polymorphism and the A allele for p53 codon 175 polymorphism were more frequently observed in these patients. When evaluating both p53 codon 72 and p53 codon 175 variants in tandem, a higher proportion of the combined CCAA genotype was observed. The presence of the C allele in the p53 codon 72 variant and the A allele in the p53 codon 175 variant may be indicative of an elevated risk for the development of odontogenic cysts. However, no significant correlations were found between the genotype distributions of p53 codon 72 and p53 codon 175 variants and factors such as patient age, sex, cyst type, cyst dimensions, and cyst position.

Conflict of interest: The authors declare that there is no potential conflict of interest.

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