ORAL DISEASES

Oral Diseases (2010) 16, 631–635. doi:10.1111/j.1601-0825.2010.01664.x

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ORIGINAL ARTICLE

Association of *P53* codon 72 polymorphism and ameloblastoma

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OBJECTIVE: To test the hypothesis that *P53* codon 72 polymorphism was associated with an increased risk of developing ameloblastoma in the Thai population.

MATERIALS AND METHODS: Seventy-eight ameloblastomas and 94 healthy controls were genotyped for the *P53* codon 72 by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

RESULTS: The frequencies of the Arg/Arg, Arg/Pro and Pro/Pro genotypes were 28.72%, 50.00% and 21.28%, respectively, in the controls; and 44.87%, 51.28% and 3.85%, respectively, in ameloblastomas. Therefore, *P53* Arg is an ameloblastoma-susceptible allele [OR (95% CI) = 2.06 (1.28–3.31), $P = 0.002$]. Sex-adjusted OR (95% CI) is 2.08 (1.29–3.34), $P = 0.002$; and adjusted OR by clinical type (95% CI) is 2.04 (1.34–3.13), $P < 10^{-3}$. Therefore, the increased risk associated with *P53* Arg may not be influenced by either the sex of patients or clinical characteristics of the tumours. Moreover, when compared with homozygous *P53* Pro, people who carried the Arg allele had a remarkably high risk of developing ameloblastoma [adjusted OR (95% CI) = 7.26 (2.34–23.41), $P < 10^{-3}$].

CONCLUSION: The Arg allele of *P53* gene codon 72 may increase susceptibility, and *P53* may be important in the aetiology of ameloblastoma.

Oral Diseases (2010) **16**, 631–635

Keywords: ameloblastoma; *P53* codon 72 polymorphism; genetic susceptibility

Introduction

Ameloblastoma is a benign odontogenic tumour that accounts for approximately 10% of all tumours that arise in the craniofacial area with unknown aetiology (Namin *et al*, 2003; Fernandes *et al*, 2005; Kumamoto and Ooya, 2006; Reichart *et al*, 2006; Mendenhall *et al*, 2007). Ameloblastomas are classified as either central or peripheral types (Regezi, 2002; Reichart *et al*, 2006; Mendenhall *et al*, 2007). Central ameloblastomas are divided into two major subtypes: conventional (solid/multicystic) types and unicystic types (Regezi, 2002; Carlson and Marx, 2006; Reichart *et al*, 2006; Mendenhall *et al*, 2007). Conventional ameloblastomas tend to be more aggressive and have a higher recurrence rate compared with unicystic ameloblastomas (Lau and Samman, 2006; LeCorn *et al*, 2006). About 92% of ameloblastomas are of the conventional type, whereas 6% are of the unicystic type and 2% are of a third type known as peripheral (Reichart *et al*, 2006). Ameloblastomas show no gender predilection, and are usually diagnosed between the fourth and fifth decades of life (except in the unicystic type, which is diagnosed between the ages of 20 and 30 years) (Reichart *et al*, 1995; Ladeinde *et al*, 2006). Ameloblastoma is benign and usually progress slowly. However, it is locally invasive, has a high recurrence rate, and may cause deformity and sometimes morbidity (Chen *et al*, 2006; Gortzak *et al*, 2006). It is believed that ameloblastic carcinoma may arise from the transformation of a benign ameloblastoma (Abiko *et al*, 2007). Wide resection beyond the radiographic border is the most generally accepted method of surgical treatment of this tumour.

The *P53* tumour suppressor gene is known to play an important role in human oncogenesis. It encodes a transcription factor which plays numerous essential functions in apoptosis, cell cycle control and maintenance of genomic integrity. Either *P53* gene mutation or *P53* genetic structure alteration as a consequence of loss of P53 function has been identified as a critical step in the malignant transformation of various tumour cells. Various polymorphisms of the *P53* gene have been reported in the general population. Polymorphism at the wild-type *P53* codon 72 of exon 4 yields either a CGC sequence coding for the amino acid Arg or a CCC sequence coding for Pro (Matlashewski *et al*, 1987;

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Received 18 September 2009; revised 16 November 2009; accepted 1 December 2009

Buchman *et al*, 1988; Ara *et al*, 1990). It is found in a region (residues 64–92) of the P53 protein that is rich in prolines; this amino acid constitutes one of five PXXP binding motifs resembling an SH3 domain. The *P53* codon 72 allelic variants have been shown to have some different biochemical and biological properties (Thomas *et al*, 1999). For example, the Arg allele induces apoptosis and represses transformation more efficiently than the Pro allele. However, the P53 Arg variant is more susceptible to degradation by the human papilloma virus (HPV) E6 protein, and is suspected to be associated with the risk of HPV-induced tumour (Storey *et al*, 1998; Ojeda *et al*, 2003).

P53 codon 72 polymorphism has been reported to be involved in susceptibility to several cancers: bladder (Chen *et al*, 2000; Soulitzis *et al*, 2002), lung (Wang *et al*, 1999; Fan *et al*, 2000), prostate (Henner *et al*, 2001), cervix (Storey *et al*, 1998; Ojeda *et al*, 2003), skin (O'Connor *et al*, 2001), oesophagus (Kawaguchi *et al*, 2000), stomach (Hiyama *et al*, 2002), liver (Yu *et al*, 1999), oral (Bau *et al*, 2007) and breast (Papadakis *et al*, 2000; Buyru *et al*, 2003). To our knowledge, an association study of ameloblastoma susceptibility has not been performed before. Therefore, in this pioneer study, we investigated the genotypic frequency at *P53* codon 72 and the associated risk in developing ameloblastoma.

Materials and methods

Sample collection

Seventy-eight paraffin-embedded samples with pathologically confirmed ameloblastoma were obtained between January 1999 and December 2008 from the Department of Oral Pathology, Faculty of Dentistry, Mahidol University. All specimens were histologically proven ameloblastoma by an oral pathologist. Clinical and radiological data were collected from the patients' files. Controls were enrolled by screening subjects from health examination clinics who had no past history of malignancy. A 6 ml peripheral blood sample was collected from each of 94 healthy controls after obtaining written informed consent. Both the ameloblastoma and control groups were of Thai population. The study was performed using a double-blind technique. Formalin-fixed, paraffin-embedded ameloblastoma tissues were sectioned into three to five sections, each 5 μM thick. Another section was stained with haematoxylin and eosin for observation to confirm pathological component. The tumour sections consisting of at least 75% tumour cells were included in the study. Without microdissection, DNA isolation was performed using the MagneSil® Genomic (Promega, Madison, WI, USA) fixed tissue system kit. DNA from the peripheral blood of each subject was extracted by proteinase K and incubated overnight at 50°C; this was followed by phenol/chloroform extraction and ethanol precipitation as described previously (Kongruttanachok *et al*, 2001; Hirunsatit *et al*, 2003). The purified genomic DNA was eluted and then used as a template in genotyping analysis.

P53 *codon 72 genotyping*

Polymorphisms at codon 72 in the *P53* gene were determined using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method with a set of primers (5′-CCCGGACGATA TTGAACA-3′ and 5′-AGAAGCCCAGACGGAAA C-3′). The PCR condition was initially denatured for 15 min at 95°C, followed by 35 cycles of 1 min at 95°C, 1 min at 57°C and 1 min at 72°C, and with a final extension at 72°C for 7 min. A 10 μl aliquot of PCR product was digested overnight at 37°C in a 15 μl reaction volume containing 10 units of *Bst*UI (New England BioLabs, Ipswich, MA, USA). After overnight digestion, the fragments were separated by electrophoresis on 2.5% agarose gel, and then stained with ethidium bromide. The Arg/Arg homozygote was cleaved by *Bst*UI, yielding 125 and 79 bp bands (Figure 1). The Pro/Pro homozygote was not cleaved by *Bst*UI and was represented by a single 204 bp band; whereas the Arg/Pro heterozygote contained all three bands (204, 125 and 79 bp) following restriction digestion. Some samples were confirmed by direct sequencing of PCR products to verify the accuracy of the genotyping.

Statistical analysis

Genotypic distributions were examined for a significant departure from the Hardy–Weinberg equilibrium by a goodness of fit chi-square test. The confidence interval (CI) test with Yates's correction was used to compare genotype frequency of *P53* gene polymorphism between ameloblastomas and controls. Some sample groups with results lower than 5 were analysed by Fisher's exact test. A *P*-value of less than 0.05 was considered to be significantly different. The odds ratio and 95% CI were calculated as an approximation of relative risk, and adjusted for confounding factors such as sex and clinical type. SPSS statistic 17.0 was used to analyse all statistical data.

Results

The genotypic data of *P53* codon 72 polymorphism are summarized in Table 1. The distribution of the genotypes among the controls was in Hardy–Weinberg equilibrium ($P > 0.05$). The *P53* codon 72 polymor-

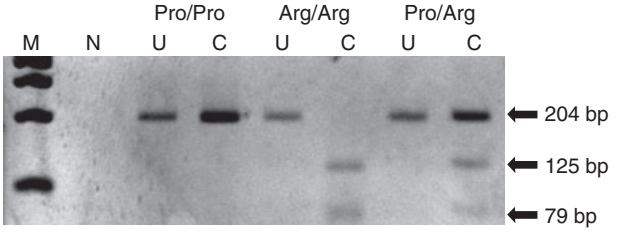

Figure 1 *P53* codon 72 genotyping by PCR-RFLP. The PCR product is digested with *BstU1* restriction enzyme and subjected to electrophoresis on a 2.5% agarose gel. The Pro/Pro homozygous allele is not digested and yielded a 204 bp band. The Arg/Arg homozygous allele is cleaved, and yielded 125 and 79 bp bands. The Arg/Pro heterozygote contains all three bands (204, 125 and 79 bp). M, 100 bp marker; N, negative control; U, PCR uncut product; C, PCR cut product

phism distribution in our control group was similar to other previous studies in Thailand (Kietthubthew *et al*, 2003; Tiwawech *et al*, 2003; Settheetham-Ishida *et al*, 2006), particularly when the control population was derived from the same area (Tiwawech *et al*, 2003).

Seventy-eight ameloblastomas (39 male, 39 female) and 94 healthy controls (55 male, 39 female) were analysed (Table 1). The mean age (± SD) of ameloblastoma patients was 36.51 ± 17.62 years, and their median age was 31 years. The mean age (± SD) of healthy controls was 33.62 ± 9.67 years, and their median age was 32 years. Ameloblastomas were categorized into unicystic type (25 cases) and conventional type (53 cases).

In ameloblastomas, the frequencies for the Arg/Arg, Arg/Pro and Pro/Pro genotypes were 44.87%, 51.28% and 3.85% respectively; and in controls the frequencies were 28.72%, 50.00% and 21.28% respectively. The Arg and Pro allele frequencies were 70.51% and 29.49% in ameloblastomas, and 53.72% and 46.28% in controls respectively. Based on these data, the Arg allele was significantly associated with the presence of ameloblastoma ($P = 0.002$), and was linked with a higher risk of ameloblastoma (crude OR = 2.06; 95% CI 1.28–3.31) when compared with the Pro allele. Moreover, people who carried the Arg allele (Arg/Pro or Arg/Arg) had a remarkably higher risk than those with homozygous Pro alleles (crude OR = 6.76; 95% CI 1.79–29.92; $P = 0.002$; and clinical adjusted OR = 7.26; 95% CI 2.34–23.41; $P < 10^{-3}$) (Table 2).

Sex and clinical type did not interfere with the P53 influence. The Arg allele resulted in increased risk in both females (OR = 2.27; 95% CI 1.12–4.64; $P = 0.021$) and males (OR = 1.92; 95% CI 0.99–3.73; $P = 0.052$). The sex-adjusted OR was 2.08 with 95% CI at 1.29–3.34 and $P = 0.002$. The effect of the Arg allele on both clinical types is also higher than in controls with no statistical significance (OR = 1.83; 95% CI 0.90–3.74; $P = 0.099$) in unicystic type and statistical significance in conventional type (OR = 2.18; 95% CI 1.27–3.76; $P = 0.004$). When clinical types were adjusted, the OR (95% CI) was 2.04 (1.34–3.13), $P < 10^{-3}$.

Discussion

Most ameloblastoma patients are diagnosed at a late stage of the disease. The mandatory treatment is wide resection at least 1 cm beyond the margin of the radiographic data. However, after the surgery, the patient will likely suffer from deformity. Early-stage ameloblastoma is difficult to diagnose because it displays mild or nonspecific clinical symptoms. Hence, the analysis of potential genetic risk factors for the prediction of ameloblastoma in patients without clinical symptoms is likely to be a valuable diagnostic strategy.

In this study we found that the Arg allele was significantly associated with the presence of ameloblastoma, and that Arg carriers had a nearly seven-fold increase in risk compared to those with Pro homozygotes. This epidemiological study suggests that the Arg allele of *P53* codon 72 is one of the genetic risk factors for ameloblastoma. In addition, this polymorphism may be useful as one of the genetic markers for predicting the occurrence of this tumour. The Arg allele of *P53* codon 72 was also used as a prognosis marker in ameloblastoma. We observed the lower odds ratio in the unicystic type than in the conventional type; the latter is highly malignant and exhibits worse prognosis. Moreover, our data may provide genetic evidence to support the importance of P53 protein in ameloblastoma development.

The *P53* gene is most extensively studied because of its role as a tumour-suppressor gene. The main function of P53 is to maintain genomic integrity with providing a protective effect against tumorigenesis. Many previous studies have investigated the association between *P53* codon 72 polymorphism and the risk of various cancers.

Table 1 *P53* codon 72 polymorphisms in ameloblastomas and healthy controls

			P53 genotypes, n *(%)*			*Allele frequency* n *(%)*	*Allelic test*		
			Arg	*Hetero*	*Pro*				
Groups	*No. of samples*	*Ave. age*	*G/G*	*G/C*	*C/C*	*G*	*OR (95% CI)*	P-*value*	*C*
Controls	94	33.6	27 (28.72%)	47 (50.00%)	20 (21.28%)	101 (53.72%)	87 (46.28%)	Ref.	
Sex									
Male	55	32.6	16 (29.09%)	29 (52.73%)	10 (18.18%)	61 (55.45%)	49 (44.55%)	Ref.	
Female	39	35.2	11 (28.21%)	18 (46.15%)	10 (25.64%)	40 (51.28%)	38 (48.72%)	Ref.	
Ameloblastoma	78	36.2	35 (44.87%)	40 (51.28%)	3 (3.85%)	110 (70.51%)	46 (29.49%)	2.06 (1.28–3.31)	0.002
Sex									
Male	39	40.2	17 (43.59%)	21 (53.85%)	1 (2.56%)	55 (70.51%)	23 (29.49%)	1.92 (0.99–3.73)	0.052
Female	39	32.8	18 (46.15%)	19 (48.72%)	2 (5.13%)	55 (70.51%)	23 (29.49%)	2.27 (1.12–4.64)	0.021
Adjust OR								2.08 (1.29–3.34)	0.002
Clinical type									
Unicystic	25	34.5	9 (36.00%)	16 (64.00%)	0 (0.00%)	34 (68.00%)	16 (32.00%)	1.83 (0.90–3.74)	0.099
Conventional	53	37.5	26 (49.06%)	24 (45.28%)	3 (5.66%)	76 (71.70%)	30 (28.30%)	2.18 (1.27–3.76)	0.004
Adjust OR								2.04 (1.34–3.13)	$< 10^{-3}$

OR, odd ratio; CI, confidence interval.

Table 2 Risk of ameloblastoma associated with *P53* codon 72 G → C genotype according to different models of inheritance

	Unicystic type OR (95% CI)	P-*value*	*Conventional type OR (95% CI)*	*P*-value	*Total type OR (95% CI)*	*P*-value	*Adjusted OR (95% CI)*	P-*value*
G dominance, C wild type								
CC	1.00		1.00		1.00		1.00	
GG or GC	14.03 (2.00–281.28)	0.069[a]	4.50 (1.18–20.18)	0.023	6.76 (1.79–29.92)	0.002	7.26 (2.34–23.41)	$<10^{-3}$
G recessive, C wild type								
CC or GC	1.00		1.00		1.00		1.00	
GG	1.40 (0.50–3.88)	0.646	2.39 (1.12–5.11)	0.022	2.02 (1.02–3.99)	0.042	1.97 (1.09–3.55)	0.024

GG and CC are the homozygous G and C respectively. GC is the heterozygous of G and C. OR, odds ratio; CI, confidence interval.
[a]Fisher exact test: two-tailed test.

However, the data are distinguishable. People who carry the Arg allele are more susceptible to develop cervical cancer (Storey *et al*, 1998; Zehbe *et al*, 2001; Ojeda *et al*, 2003), breast cancer (Papadakis *et al*, 2000) and hepatocellular carcinoma (Yu *et al*, 1999), whereas those who carry the Pro allele are more susceptible to develop bladder cancer (Chen *et al*, 2000) and lung cancer (Wang *et al*, 1999; Fan *et al*, 2000). Recent studies indicated that the Arg allele is preferentially mutated and retained in various human cancers arising in Pro/Arg heterozygotes (Brooks *et al*, 2000; Marin *et al*, 2000). The Arg variant may enhance mutant P53 binding to P73, thus neutralizing P73-induced apoptosis rather than the Pro variant (Brooks *et al*, 2000; Marin *et al*, 2000), which enhances tumorigenesis and provides a selective growth advantage to tumour cells (Tada *et al*, 2001). Kumamoto *et al* (2004) reported high frequency of increased P53 expression compared to tooth germ, suggesting a role in ameloblastoma etiology.

Identifying genetic susceptibility implies what may be an environmental factor promoting the disease. In an *in vitro* study, the P53 Arg variant induced apoptosis with faster kinetics more efficiently than the P53 Pro variant (Thomas *et al*, 1999). However, it has been proposed that the P53 Arg variant is more easily degraded by the HPV E6 protein (Storey *et al*, 1998; Ojeda *et al*, 2003). Interestingly, a significant association between HPV and ameloblastoma has been reported (Namin *et al*, 2003). However, ameloblastoma cases reported by Namin *et al* were positive for mainly low risk HPV type 6. There should be further investigation to explore if there is a mechanical relationship between the P53 variant and HPV in ameloblastoma.

Acknowledgements

The authors are grateful to Mr Dusit Bumalee for excellent technical assistance. This work was supported by the Center of Excellence in Molecular Genetics of Cancer and Human Diseases, Department of Anatomy, Faculty of Medicine, Chulalongkorn University, TRF-MRG young scientific researcher grant No. MRG5180242 and TRF senior research scholar grant.

Author contributions

N Kitkumthorn contributed to the study concepts, study design, definition of intellectual content and to manuscript preparation. P Yanatatsaneejit, J Rabalert and C Dhammawipark conducted the experiment and analysed the data. A Mutirangura contributed to data analysis, manuscript editing and review.

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