RESEARCH





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Abstract

Background Recently, a systematic review and meta-analysis demonstrated that overexpression of p53 immunoprotein was significantly associated with progression risk of oral potentially malignant disorders (OPMD). However, the results of investigations on TP53 genetic typing in OPMD were inconsistent and inconclusive.

Methods A systematic evaluation was conducted to identify all eligible case–control studies on the association of TP53 codon 72 polymorphism with both onset and progression of OPMD.

Results A total of 768 OPMD patients and 1173 healthy individuals were identified from 12 eligible case–control studies on TP53 codon 72 polymorphism OPMD onset. In overall and subgroup analyses, no significantly risk of OPMD onset was observed in the cases for genetic models including allele C vs. G, homozygote CC vs. GG, heterozygote GC vs. GG, dominant GC + CC vs. GG, and recessive CC vs. GG + GC (all *P*-value of association test > 0.05). Further, a total of 465 OPMD patients and 775 oral squamous cell carcinoma (OSCC) ones were identified from 8 eligible case–control studies on this polymorphism in OPMD progression to OSCC. The analyses revealed that there was also no significantly risk of OPMD progression in the cases for the genetic models (all *P*-value of association test > 0.05).

Conclusion Our data of a pooled-analysis indicates that TP53 codon 72 polymorphism may not act as genetic factor for the risk of OPMD onset and progression. Combined with the conclusion by a systematic review and meta-analysis, we put forward a new opinion that TP53 genetic typing cloud not influence p53 protein expression in OPMD.

Keywords Oral potentially malignant disorders, Oral cancer, TP53, Meta-analysis, Single-nucleotide polymorphisms

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Introduction

Oral potentially malignant disorders (OPMD) contain a group of lesions such as oral leukoplakia (OLK), oral erythroplakia, oral lichen planus, and oral submucous fibrosis, which carry a significantly increased risk for malignant progression to oral squamous cell carcinoma (OSCC) [1]. The onset and progression of OPMD arise as a result of a multi-step carcinogenic process that correlates to the accumulation of genetic and epigenetic alterations [2]. Single nucleotide polymorphisms (SNP) in gene encoding for susceptibility factors may influence gene expression, protein function, and disease predisposition [3]. Although the etiology and progression of OPMD are quite complex, evidence indicates that single-nucleotide polymorphisms of candidate genes may be associated with genetic susceptibility of the disorders [4, 5].

Tumor suppressor p53 (TP53) gene is regarded as potential guardian of the human genome [6]. TP53 is the most common mutated gene in head and neck cancer, making p53 an appealing target for improving treatment of head and neck cancer by restoring its tumor suppressor action [7, 8]. The rs1042522 G/C polymorphism of TP53 results in the alteration at codon 72 between arginine (Arg) and proline (Pro) and causes the TP53Arg-72Pro mutation. This may affect the normal function of the TP53 protein and is implicated in susceptibility to several cancers including OSCC [9-11]. A earlier metaanalysis published in BMC Oral Healthreported TP53 codon 72 polymorphism was not associated with OLK susceptibility [12]. Recently, a systematic review and meta-analysis demonstrated that overexpression of p53 immunoprotein was significantly associated with the risk of OPMD malignant progression [13].

Based on the above, we hypothesize that TP53 polymorphism may be associated with the risk of OPMD progression to OSCC. Besides, there are newly published several case–control studies on various types of OPMD, which are suitable to assess the association of TP53 codon 72 polymorphism with the onset of general OPMD. Therefore, the objective of the meta-analysis was to systematically evaluate the relationship between TP53 codon 72 polymorphism and both onset and progression of OPMD based on case–control studies.

Materials and methods

Search strategy and data extraction

A comprehensive literature search was conducted on PubMed, Web of Science, and Medline databases for all relevant publications on the association between TP53 codon 72 polymorphism and OPMD, without any restriction on Feb. 21, 2023. According to the search strategy described in Supplementary Table S1, we used medical subject term ("polymorphism*" OR "gene variant") AND ("p53 OR "TP53") AND the synonyms of OPMD in all fields. The inclusion criteria for eligible articles were as follows: (i) human case–control studies; (ii) evaluation of TP53 codon 72 polymorphism and OPMD onset or progression. OPMD progression indicates the polymorphism in OPMD compared with in OSCC; (iii) sufficient genotyping data for the computation of odds ratio (OR) and 95% confidence interval (CI); (iv) histologically confirmed diagnosis of OPMD and OSCC. On the contrary, the exclusion criteria were as follows: (i) not a case–control study; (ii) overlapping or duplicate publications; (iii) no genotype data reported.

According to the selection criteria, all relevant crude data were extracted from each eligible study independently by two investigators. Inconsistency was discussed until a consensus was obtained with a third investigator. The following information were extracted from each study: first author' name, publication year, country origin, ethnicity, age, sex, tobacco and alcohol use, genotyping methods, number and characteristics of cases and controls, genotype distributions of cases and controls. The case group was OPMD, and control group was healthy individuals or OSCC. Ethical approval and informed consent were not applicable for a meta-analysis. Base on the above process and the flow diagram of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Supplementary Figure S1), 13 eligible case-control studies on TP53 codon 72 polymorphism and OPMD onset or progression were retrieved for detailed evaluation from the literature databases (Table 1) [14-26].

Statistical analysis

As per the methods described previously [27], the statistical analysis was carried out with the software Review manager 5.4 (The Cochrane Collaboration, Oxford, UK). Hardy-Weinberg equilibrium (HWE) of control group in included studies was measured using Pearson's goodnessof-fit χ^2 test. The strength of association of TP53 codon 72 polymorphism and OPMD onset or progression was determined by calculating odds ratios (ORs) with corresponding 95% credible interval (CI). χ^2 -based Q-test and I² statistics were utilized to test statistical heterogeneity, and the Z-test was used to assess the statistical significance of the pooled OR. ORs were pooled according to the fixed-effects model (Mantel-Haenszel model) if heterogeneity was not significant (P > 0.05). Otherwise, the random-effects model (DerSimonian and Laird model) was conducted. Begg's funnel plot and Egger's test were visually examined to evaluate the potential publication bias of the included studies. All tests were used two-sided *P* value, and the value less than 0.05 was accepted as statistical significance.

Author, Year	Country	Ethnicity	Study design	Mean age (y)	Male (%)	Tobacco (%)	Alcohol (%)	Genotyping method	HWE (P value)
Mitra et al. 2005	India	Asian	342 HC ^a	50.4	76.1	53.4	46.5	PCR-RFLP	0.444
[14]; Misra et al. 2009 [15]			191 OLK	47	86.3	96.5	15.7		
2009 [15]			308 OSCC	55	63.5	43.2	18.4		
Lin et al. 2008 [16]	China	Asian	280 HC	52.1	47.5	15.7	21.1	PCR-RFLP	0.328
			39 OSF	43.1	100	94.9	59		
			70 OLK	49.8	92.9	81.4	82.9		
			297 OSCC	49.5	92.6	81.5	68.4		
Ye et al. 2008 [17]	USA	Mixed	137 HC	59.1	55.8	44.9	68	PCR-RFLP	0.532
			110 OLK	57.4	55.8	68.7	53.7		
Ghabanchi et al.	Iran	Asian	93 HC	46.7	43	NA	NA	PCR-SSP	0.001
2009 [18]			25 OLP	43.1	44	NA	NA		
Yanatatsaneeji	Thailand	Asian	94 HC	33.6	32.6	NA	NA	PCR-RFLP	0.999
et al. 2010 [<mark>19</mark>]			97 OLP	36.2	53.2	NA	NA		
Sikka et al. 2014	India	Asian	98 HC	49	87	59.3	NA	PCR-RFLP	0.479
[20]			86 OLK	48	90.1	45	NA		
Zarate et al. 2017	Argentina	Mixed	18 HC	NA	50	NA	NA	PCR-RFLP	0.139
2arate et al. 2017 [21]			30 OLP	NA	33	NA	NA		
			14 OLK	NA		NA	NA		
			44 OSCC	NA	63	NA	NA		
Ramya et al. 2017	India	Asian	25 HC	NA	NA	36	NA	PCR-RFLP	0.982
[22]			15 OLK	46.7	80	60	NA		
Tandon et al.	India	Asian	21 HC	NA	NA	NA	NA	PCR-RFLP	0.879
2017 [23]			6 OLK	NA	82.9	NA	NA		
			35 OSCC	NA		NA	NA		
Tabatabaei et al.	Iran	Asian	30 OLP	43.3	21.1	NA	NA	PCR	0.616
2018 [24]			20 OSCC	58.2	39.3	NA	NA		
Hallikeri et al.	India	Asian	30 HC	NA	86.7	NA	NA	PCR	0.219
2019 [25]			30 OSF	NA	100	NA	NA		
			30 OSCC	NA	86.7	NA	NA		
Galíndez et al.	Argentina	a Mixed	35 HC	NA	39.5	21.1	31.6	PCR-RFLP	0.953
2021 [26]			55 OLK/OLP	NA	37.7	73.8	31.1		
			41 OSCC	NA	65.9	57.6	60.6		

 Table 1
 The characteristics of the included case-control studies on p53 protein codon 72 polymorphism in onset and progression of OPMD

HC health control, HWE Hardy–Weinberg equilibrium, OLK oral leukoplakia, OLP oral lichen planus, OPMD oral potentially malignant disorders, OSCC oral squamous cell carcinoma, OSF oral submucous fibrosis, PCR polymerase chain reaction, PCR–RFLP PCR-restriction fragment length polymorphism, PCR-SSP PCR-single-specific primer

^a The 2 studies used the same health control group (n = 342)

Results

Association of TP53 codon 72 polymorphism with OPMD onset

There were 12 eligible case–control studies on TP53 codon 72 polymorphism in OPMD onset, compare to health control (Table 1). A total of 768 OPMD patients and 1173 healthy individuals were identified from six countries including India, China, USA, Argentina, Iran, and Thailand. In the overall analysis, no significantly increased or decreased risk of OPMD onset was observed in the cases for the five genetic models including allele C

vs. G [P_A (P-value of association test)=0.39], homozygote CC vs. GG (P_A =0.55), heterozygote GC vs. GG (P_A =0.76), dominant GC+CC vs. GG (P_A =0.27), and recessive CC vs. GG+GC (P_A =0.83). In the stratified analysis by ethnicity, the similar results were observed in five genotype models among Asians and mixed ethnicity. The detailed genotype distributions and forest plots of the five genetic models are depicted in Fig. 1. Begg's funnel plot showed that there was no obvious evidence for publication bias in five genetic models of TP53 codon 72 polymorphism in OPMD onset (Figure S2). These results

Α	Allele model Study or Subgroup	OPMI Events	D Total	HC Events	Total	Weight M	Odds Ratio 4-H, Random, 95% C	а	M-H	Odds Ratio I, Random, 95	% CI	
	2.1.1 Asian Ghabanchi et al, 2009	22	50	102	186	9.0%	0.65 [0.35, 1.21	1		-		
	Hallikeri et al, 2019 Lin et al, 2008	23 96	60 218	16 264	60 560	7.8% 11.8%	1.71 [0.79, 3.70 0.88 [0.64, 1.21]		+		
	Mitra et al, 2005; Misra et al, 2009 Ramya et al, 2017	156 17	382 30	355 26	684 50	12.2% 6.7%	0.64 [0.50, 0.82 1.21 [0.49, 3.00	!])]				
	Sikka et al, 2014 Tandon et al, 2017	106 3	172 12	99 17	196 42	10.9% 3.8%	1.57 [1.04, 2.38 0.49 [0.12, 2.08	[] []	_			
	Yanatatsaneeji et al, 2010 Subtotal (95% CI)	126	194 1118	87	188 1966	11.0% 73.2%	2.15 [1.43, 3.25 1.07 [0.73, 1.58]]		•		
	Heterogeneity: Tau ² = 0.22; Chi ² = 3 Test for morell effort: 7 = 0.26 (B = 6	549 5.07, df	= 7 (P <	966); I ² =	80%						
	2.1.2 Mixed).72)										
	Galindez et al, 2017 Ye et al. 2008	52	110	26	70	9.2%	1.52 [0.82, 2.80)] 11		_ _		
	Zarate et al, 2017 Subtotal (95% CI)	44	88 418	7	36	6.6% 26.8%	4.14 [1.64, 10.45) 1		_	-	
	Total events Heterogeneity: Tau ² = 0.54; Chi ² = 1	150 3.19, df	= 2 (P =	118	1 ² = 8	5%						
	Test for overall effect: Z = 0.91 (P = 0	0.36)										
	Total (95% CI) Total events	699	1536	1084	2346	100.0%	1.16 [0.83, 1.62			•		
	Test for overall effect: Z = 0.86 (P = 0 Test for subgroup differences: Chi ² =	0.39, df 0.49, df	= 10 (P	< 0.000	1 ² = 01	= 79%		0.01	0.1	с ^і с	10	100
В	Heterozygote model	OPN	4D	н	:	•	Odds Ratio			Odds Ratio		
	Study or Subgroup 2.1.1 Asian	Events	Total	Events	Tota	l Weight	M-H, Fixed, 95% Cl		м-	H, Fixed, 959	S CI	
	Ghabanchi et al, 2009 Hallikeri et al, 2019	6 7	17	14	20	9 3.0% 5 3.2%	1.36 [0.42, 4.40] 1.05 [0.31, 3.57]					
	Mitra et al, 2005; Misra et al, 2009 Ramua et al, 2017	92	159	152	24	4 34.0%	0.73 [0.49, 1.11]			-	_	
	Sikka et al, 2017 Sikka et al, 2014	38	52	55	70	5 1.7% 5 7.7% 7 1.5%	1.04 [0.47, 2.29]		_		_	
	Yanatatsaneeji et al, 2010 Subtotal (95% CI)	36	52 410	47	72	4 7.7% 8 77.3%	1.29 [0.61, 2.75] 0.93 [0.72, 1.20]	1		+		
	Total events Heterogeneity: Chi ² = 2.64, df = 7 (F	251 = 0.92)	: I ² = 0	456						1		
	Test for overall effect: Z = 0.57 (P =	0.57)										
	2.1.2 Mixed Galindez et al, 2021	38	48	16	3	2.6%	3.33 [1.22, 9.04]	1				
	Ye et al, 2008 Zarate et al, 2017 Subtotal (05% CI)	42 24	104	53	12	1 18.8% 5 1.3%	0.87 [0.51, 1.48] 5.20 [1.30, 20.85]					-
	Total events Heterogeneity: Chi ² = 0.40, df = 3.47	104	0). I ₅	72	10	. 22.1%	1.40 [0.91, 2.15]					
	Test for overall effect: Z = 1.54 (P =	0.12)	.,	. 370								
	Total (95% CI) Total events	355	606	528	89	5 100.0%	1.04 [0.83, 1.29]	1		+		
_	Heterogeneity: Chi ² = 14.17, df = 10 Test for overall effect: Z = 0.31 (P =	0 (P = 0.1 0.76)	17); I ² =	29%				0.01	0.1	GG ¹ GC	10	100
С	Homozygote model	OPME	f = 1 (P)	= 0.11) HC	(* =) Total	Weight M	Odds Ratio			Odds Ratio		
	2.1.1 Asian Ghabanchi et al. 2009	8	19	44	79	10.2%	0.58 [0.21, 1.59]		M-D,	Kandolii, 937		
	Hallikeri et al, 2019 Lin et al, 2008	8 17	23 47	4 56	23 128	8.3% 12.0%	2.53 [0.64, 10.05] 0.73 [0.37, 1.45]			+	_	
	Mitra et al, 2005; Misra et al, 2009 Ramya et al, 2017	32 5	99 8	98 7	183 13	12.8% 6.4%	0.41 [0.25, 0.69] 1.43 [0.24, 8.64]		_		_	
	Sikka et al, 2014 Tandon et al, 2017	34 0	48	22	43	11.0%	2.32 [0.98, 5.50] 0.27 [0.01, 6.46]	_			-	
	Subtotal (95% CI)	149	308	20	528	74.9%	1.14 [0.56, 2.32]			+		
	Heterogeneity: Tau ² = 0.70; Chi ² = 29 Test for overall effect: Z = 0.36 (P = 0	.57, df = .72)	= 7 (P =	0.0001)	; 1 ² = 3	6%						
	2.1.2 Mixed	7	17	ç	10	8 1%	1 96 [0 48 7 99]				_	
	Ye et al, 2008 Zarate et al, 2017	6 10	68 20	16 2	84 15	10.3%	0.41 [0.15, 1.12] 6.50 [1.16, 36,58]					_
	Subtotal (95% CI) Total events	23	105	23	118	25.1%	1.54 [0.31, 7.70]			-	-	
	Heterogeneity: Tau ² = 1.52; Chi ² = 8. Test for overall effect: Z = 0.53 (P = 0	42, df = .60)	2 (P = 0	0.01); I ² =	= 76%							
	Total (95% CI) Total events	172	413	278	646	100.0%	1.20 [0.65, 2.23]			+		
	Heterogeneity: Tau ² = 0.70; Chi ² = 38 Test for overall effect: Z = 0.59 (P = 0	.09, df = .55)	10 (P -	< 0.0001	1); I ² =	74%		0.01	0.1	66 CC	10	100
n	Test for subgroup differences: Chi ² = 0	0.12, df =	= 1 (P = D	0.73), l ⁱ HC	² = 0%		Odds Ratio			Odds Ratio		
	Study or Subgroup 2.1.1 Asian	Events	Total I	Events	Total	Weight M	-H, Random, 95% CI		М-Н,	Random, 95%	CI	
	Ghabanchi et al, 2009 Hallikeri et al, 2019	14	25 30	58 12	93 30	8.9% 7.9%	0.77 [0.31, 1.88] 1.50 [0.54, 4.17]			<u> </u>		
	Lin et al, 2008 Mitra et al, 2005; Misra et al, 2009 Ramua et al, 2017	79 124	109	208	280 342	12.7%	0.91 [0.55, 1.50] 0.61 [0.42, 0.90]			-		
	Sikka et al, 2014 Tandon et al. 2017	72	86	77	98 21	10.2%	1.40 [0.66, 2.97] 0.62 [0.10, 3.82]			-		
	Yanatatsaneeji et al, 2010 Subtotal (95% CI)	81	97 559	67	94 983	10.7% 72.7%	2.04 [1.02, 4.10] 1.01 [0.71, 1.44]			+		
	Total events Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 12$ Test for overall effect: $Z = 0.07$ ($R = 1$)	400 L.90, df =	= 7 (P =	711 0.10); I ²	= 415	6						
	2.1.2 Mixed											
	Galíndez et al, 2017 Ye et al, 2008	45 48	55 110	21 69	35 137	8.3% 12.6%	3.00 [1.15, 7.86] 0.76 [0.46, 1.26]			+	_	
	Zarate et al, 2017 Subtotal (95% CI)	34	209	5	18 190	6.3% 27.3%	8.84 [2.53, 30.84] 2.50 [0.59, 10.62]			-	-	
	Heterogeneity: Tau ² = 1.41; Chi ² = 16 Test for overall effect: Z = 1.24 (P = 0	5.24, df = 0.21)	= 2 (P =	95 0.0003)	; I ² = 4	38%						
	Total (95% CI)		768		1173	100.0%	1.26 [0.84, 1.88]			•		
	Total events Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 30$ Test for overall effect: $T = 1.10$ (R = 0.000)	527).28, df =	= 10 (P	= 0.0001	8); I ² =	67%		0.01	0.1	1	10	100
_	Test for subgroup differences: Chi ² =	1.42, df	= 1 (P =	0.23), 1	² = 29	.4%				66 00+60		
E	Recessive model Study or Subgroup 2.1.1 Asian	Events	Total E	HC vents T	otal N	Weight M-	H, Random, 95% Cl		М-Н, R	andom, 95% (1	
	Ghabanchi et al, 2009 Hallikeri et al, 2019	8 8	25 30	44 4	93 30	9.9% 7.5%	0.52 [0.21, 1.33] 2.36 [0.63, 8.92]		_	+	-	
	Lin et al, 2008 Mitra et al, 2005; Misra et al, 2009 Ramma et al, 2017	17 32	109	56 98	280 342	12.2%	0.74 [0.41, 1.34] 0.50 [0.32, 0.78]		-	-		
	Sikka et al, 2017 Sikka et al, 2014 Tandon et al, 2017	34	86	22	23 98 21	11.9%	2.26 [1.19, 4.29]					
	Yanatatsaneeji et al, 2010 Subtotal (95% CI)	45	97 559	20	94 983	11.9% 76.3%	3.20 [1.70, 6.04] 1.14 [0.60, 2.14]			+		
	Total events Heterogeneity: $Tau^2 = 0.58$; $Chi^2 = 33$ Tatt for overall effort: $3 = 0.20$ (2)	149 .46, df =	7 (P < 0	255 0.0001);	l ² = 7	9%						
	2.1.2 Mixed											
	Galindez et al, 2017 Ye et al, 2008	7	55 110	5 16	35 137	8.0% 9.7%	0.88 [0.25, 3.01] 0.44 [0.16, 1.16]		_	-	_	
	Zarate et al, 2017 Subtotal (95% CI) Total events	23	44 209	2	18 190	6.0% 23.7%	2.35 [0.46, 12.01] 0.81 [0.33, 1.98]		-	•		
	Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 3.1$ Test for overall effect: $Z = 0.47$ (P = 0.	4, df = 2 .64)	2 (P = 0.	.21); I ² =	36%							
	Total (95% CI) Total events	172	768	278	173 1	00.0%	1.06 [0.63, 1.79]			+		
	Heterogeneity: $Tau^2 = 0.50$; $Chi^2 = 37$ Test for overall effect: $Z = 0.22$ (P = 0.	34, df = 83)	10 (P <	0.0001); I ² =	73%		0.01	0.1 GG+	GC ¹ CC	10	100
	Test for subgroup differences: $Chi^2 = 0$.37. df =	1 (P =	U.54), P	= 0%							

Fig. 1 Detailed genotype distributions and forest plots of TP53 codon 72 polymorphism with OPMD onset compared to healthy control (HC) in five genetic models. **A** allele C vs. G, **B** heterozygote GC vs. GG, **C** homozygote CC vs. GG, **D** dominant GC + CC vs. GG, **E** recessive CC vs. GG + GC

indicate that TP53 codon 72 polymorphism may have no significant influence on the risk of OPMD onset.

Association of TP53 codon 72 polymorphism with OPMD progression

There were 8 eligible case-control studies on TP53 codon 72 polymorphism in OPMD progression to OSCC (Table 1). A total of 465 OPMD patients and 775 OSCC ones were identified from four countries including India, China, Argentina, and Iran. In the overall analysis, no significantly increased or decreased risk of OPMD progression to OSCC was observed in the cases for the five genetic models including allele C vs. G $[P_A = 0.10]$, homozygote CC vs. GG ($P_A = 0.19$), heterozygote GC vs. GG ($P_A = 0.44$), dominant GC+CC vs. GG $(P_A = 0.48)$, and recessive CC vs. GG+GC $(P_A = 0.48)$. In the stratified analysis by ethnicity, the similar results were observed in four genotype models among Asians and mixed ethnicity. Constrainedly, an association of TP53 codon 72 polymorphism in allele model with OPMD progression was found (OR, 1.20; 95%CI, 0.98-1.45; P = 0.069) among Asians based on 6 studies. The detailed genotype distributions and forest plots of the five genetic models are illustrated in Fig. 2. Begg's funnel plot showed that there was no obvious evidence for publication bias in five genetic models of TP53 codon 72 polymorphism in OPMD progression (Figure S3). These results indicate that TP53 codon 72 polymorphism may have no significant influence on the risk of OPMD progression to OSCC.

Discussion

Given the fact that TP53 exhibits diverse behaviors and is involved in various regulatory roles during carcinogenesis, elucidating the role of wild-type and mutated TP53 in the development of OSCC remains a challenge [5–8]. In an updated meta-analysis, Sun et al. [12] conducted an updated meta-analysis of 17 case–control studies from 16 articles with 3047 cases of OSCC and 3305 health controls, and concluded that there was no significant association between TP53 codon 72 polymorphism and the risk of OSCC in either the Asian or Caucasian population. This data was in agreement with the result from another contemporaneous meta-analysis [28]. Interestingly, Sun et al. [12] performed an additional meta-analysis of 6 case–control studies from 5 articles with 391 cases

A	Allele model Study or Subgroup	OSC Events	C Total	OPM Events	D Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% Cl
	Hallikeri et al, 2019 Lin et al, 2008 Mitra et al, 2005; Misra et al, 2009 Tabatabaei et al, 2018 Tandon et al, 2017 Subtotai (95% CI) Total events Heterogeneity: Chi ² = 8.64, df = 4 (F Test for overall effect: Z = 1.79 (P =	22 247 287 24 34 614 • = 0.07); 0.07)	60 594 616 56 70 1396 $I^2 = 54$	23 62 156 7 3 251	60 140 382 38 12 632	6.7% 26.9% 47.3% 2.2% 1.2% 84.3%	0.93 [0.44, 1.95] 0.90 [0.62, 1.30] 1.26 [0.98, 1.64] 3.32 [1.25, 8.82] 2.83 [0.71, 11.35] 1.20 [0.98, 1.45]	
	1.1.2 Mixed Galindez et al, 2017 Zarate et al, 2017 Subtotal (95% C1) Total events Heterogeneity: Chi ² = 0.14, df = 1 (F Test for overall effect: Z = 0.00 (P	40 41 81 = 0.71); 1.00)	82 88 170 I ² = 09	52 14 66	110 28 138	10.5% 5.2% 15.7%	1.06 [0.60, 1.88] 0.87 [0.37, 2.04] 1.00 [0.62, 1.61]	•
	Total (95% CI) Total events Heterogeneity: Chi ² = 9.21, df = 6 (F Test for overall effect: Z = 1.65 (P Test for subgroup differences: Chi ² =	695 9 = 0.16); 0.10) 0.47, df	1566 $I^2 = 35$ = 1 (P	317 5% = 0.49),	770	100.0% %	1.16 [0.97, 1.40]	0.01 0.1 G C 10 100
B	Heterozygote model Study or Subgroup	OSC Events	C Total	OPM Events	D Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% Cl
	1.1.1 Asian Hallikeri et al, 2019 Line et al, 2008 Mirra et al, 2008; Misra et al, 2009 Tabatabaei et al, 2018 Tandon et al , 2017 Subtotal (95% CD) Total events Heterogeneity: Ch ² = 9.41, df = 4 (f Test for overall effect: Z = 1.04 (P =	26 155 155 20 20 376 = 0.05); 0.30)	34 251 242 26 28 581 $I^2 = 57$	38 62 92 7 3 202 7%	48 92 159 19 6 324	7.3% 34.3% 39.5% 1.8% 1.4% 84.4%	0.86 [0.30, 2.46] 0.78 [0.47, 1.29] 1.30 [0.86, 1.95] 5.71 [1.55, 21.06] 2.50 [0.41, 15.10] 1.17 [0.87, 1.55]	• • •
	1.1.2 Mixed Galindez et al, 2021 Zarate et al, 2017 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0.01, df = 1 (f Test for overall effect: Z = 0.51 (P =	26 23 49 9 = 0.93); 0.61)	34 35 69 I ² = 09	38 24 62	48 34 82	7.3% 8.3% 15.6%	0.86 [0.30, 2.46] 0.80 [0.29, 2.20] 0.83 [0.40, 1.71]	•
	Total (95% CI) Total events Heterogeneity: Chi ² = 10.14, df = 6 Test for overall effect: Z = 0.78 (P Test for subgroup differences: Chi ² =	425 (P = 0.12) 0.44) 0.74, df	650); I ² = 4 = 1 (P	264 \$1% = 0.39).	406	100.0% %	1.11 [0.85, 1.45]	0.01 0.1 0.1 cc cc
С	-Homozygote model	oscc		OPMD			Odds Ratio	Odds Ratio
	Judy or service Hallkeri et al. 2019 Line tal. 2008 Mitra et al. 2005: Misra et al. 2009 Tabatabaei et al. 2018 Subbotal (\$95(C)) Total events Heterogeneity. Chi ² = 4.67, df = 4 (P Test for overall effect Z = 1.47 (P = 6	10 46 66 2 7 131 = 0.32); l ² 0.14)	28 142 153 8 15 346 * = 14%	8 17 32 0 0 57	23 47 99 12 3 184	10.3% 31.4% 40.1% 0.5% 9 0.8% 6 83.0%	1.04 [0.33, 3.31] 0.85 [0.42, 1.69] 1.59 [0.94, 2.70] 1.52 [0.40, 231.42] 1.18 [0.27, 140.10] 1.33 [0.91, 1.96]	
	1.1.2 Mixed Galindez et al, 2017 Zarate et al, 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0.29, df = 1 (P = 0 Test for overall effect: Z = 0.14 (P = 0	7 9 16 = 0.59); I ² 0.89)	15 21 36 ² = 0%	7 10 17	17 20 37	6.4% 10.6% 17.0%	1.25 [0.31, 5.07] 0.75 [0.22, 2.57] 0.94 [0.37, 2.35]	
	Total (95% CI) Total events Heterogeneity: Chi ² = 5.37, df = 6 (P Test for overall effect: Z = 1.31 (P = C Test for subgroup differences: Chi ² =	147 = 0.50); l ² 0.19) 0.48, df =	382 ² = 0% 1 (P =	74 0.49), l ²	221 1	.00.0%	1.27 [0.89, 1.80]	01 0.1 1 10 100 GG CC
כ	Dominant model Study or Subgroup	OSCC Events	Fotal E	OPMD vents	fotal N	Weight N	Odds Ratio 1-H, Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl
	Halikeri et al. 2019 Lin et al. 2008 Mira et al. 2005; Misra et al. 2009 Tabatabaei et al. 2018 Tandon et al. 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.27; Ch ² = 11 Test for overall effect: 2 = 1.02 (P = c	12 201 221 22 27 483 2.04, df =	30 297 308 28 35 698 4 (P =	15 79 124 7 3 228 0.02); I ²	30 109 191 19 355 = 67%	12.2% 23.1% 25.5% 8.9% 5.4% 75.0%	0.67 [0.24, 1.85] 0.80 [0.49, 1.29] 1.37 [0.93, 2.02] 6.29 [1.72, 23.01] 3.38 [0.57, 20.10] 1.37 [0.75, 2.51]	→ + + +
	1.1.2 Mixed Galindez et al, 2017 Zarate et al, 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 0. Test for overall effect: $Z = 0.47$ ($P = 0$	33 32 65 05, df = 1 0.64)	41 44 85 L (P = 0	45 34 79 .83); I ² =	55 44 99 = 0%	12.0% 13.0% 25.0%	0.92 [0.33, 2.57] 0.78 [0.30, 2.07] 0.84 [0.42, 1.71]	
	Total events Heterogeneity: Tau ² = 0.17; Chi ² = 1: Test for overall effect: Z = 0.71 ($P = 0$ Test for subgroup differences: Chi ² =	548 2.87, df =).48) 1.04, df =	783 6 (P = 1 (P =	307 0.05); I ² 0.31), I ³	454 1 = 53%	6	1.18 [0.75, 1.86]	0.01 0.1 cG cC+GC 10 100
Ξ	Recessive model	OSCO	; Total	OPME Events) Total	Weight /	Odds Ratio M-H, Random. 95% CI	Odds Ratio M-H, Random. 95% CI
	L.1.1 Asia Halikeri et al, 2019 Lin et al, 2008 Mirra et al, 2008 Mirra et al, 2008 Tabatabaei et al, 2018 Tandon et al, 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² e - 1.0.2 / 0 - 1 Test for overall effort: 7 - 1.0.2 / 0 -	12 201 221 22 27 483 2.04, df = 0.31)	30 297 308 28 35 698 4 (P =	15 79 124 7 3 228 0.02); i	30 109 191 19 355 ¹ = 679	12.2% 23.1% 25.5% 8.9% 5.4% 75.0%	0.67 [0.24, 1.85] 0.80 [0.49, 1.29] 1.37 [0.93, 2.02] 6.29 [1.72, 23.01] 3.38 [0.57, 20.10] 1.37 [0.75, 2.51]	••••••••••••••••••••••••••••••••••••••
	rest for overall effect: $Z = 1.02$ (P = 1.1.2 Mixed Calindez et al, 2017 Zarate et al, 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 0 Test for overall effect: $Z = 0.47$ (P =	33 32 65 .05, df = 0.64)	41 44 85 1 (P = 0	45 34 79 0.83); I ²	55 44 99 = 0%	12.0% 13.0% 25.0%	0.92 [0.33, 2.57] 0.78 [0.30, 2.07] 0.84 [0.42, 1.71]	-
	Total (95% CI) Total events Heterogeneity: Tau ² = 0.17; Chi ² = 1 Test for overall effect: $Z = 0.71$ (P = Test for subgroup differences: Chi ² =	548 2.87, df = 0.48) 1.04, df =	783 6 (P =	307 0.05); l ⁱ	454 ² = 539 ² = 4 2	100.0% ;	1.18 [0.75, 1.86]	0.01 0.1 1 10 100 GG CC+GC

Fig. 2 Detailed genotype distributions and forest plots of TP53 codon 72 polymorphism with OPMD progression to OSCC in five genetic models. A allele C vs. G, B heterozygote GC vs. GG, C homozygote CC vs. GG, D dominant GC + CC vs. GG, E recessive CC vs. GG + GC

of OLK and 763 health controls, and also found that no significant association of TP53 codon 72 polymorphism with OLK susceptibility. In this study, we highlighted the potential role of TP53 codon 72 polymorphism in the risk of onset and progression of general OPMD (containing OLK, oral lichen planus, and oral submucous fibrosis) through a pooled-analysis of 13 case–control studies. Overall, the results of this study indicated that TP53 codon 72 polymorphism may not also be associated with the risk of OPMD onset and progression.

Recently, overexpression of p53 immunoprotein was demonstrated to be significantly associated with malignant progression of OPMD [13]. This was inconsistent with the result of TP53 codon 72 polymorphism not associated with OPMD progression in this study, suggesting p53 overexpression in OPMD progression could be not influenced by TP53 codon 72 polymorphism. Tandon et al. examined TP53 codon 72 gene polymorphism and p53 immunoexpression in 6 cases of OLK and 35 cases of OSCC, but they did not investigate the relationship between TP53 polymorphism and p53 immunoexpression in two groups. Zhang et al. [29] reported that p53 protein expression was identified to be affected by TP53 codon 72 polymorphism in low rectal cancer. Dastjerdi MN [30] reported that TP53 codon 72 polymorphism may be correlated with p53 overexpression and increased risk for colorectal cancer. Al-Dhaheri et al. [31] reported that p53 overexpression in the progression towards malignancy of preneoplastic and neoplastic rat mammary glands associated with TP53 polymorphism; while Rybárová et al. [32] reported that no statistically significant difference was found between TP53 codon 72 polymorphism and p53 protein expression in human breast cancer. These variations in results might be possible due to organ specificity and species differences.

Meta-analysis allows stronger quantitative synthesis for identifying some models of risk markers, and reduces the limitations of the relatively small sample size and sampling bias of individual studies [12, 28]. Although the efforts in performing a comprehensive analysis, certain limitations need to be addressed in this study. First, the number of eligible studies available with the pooled sample size of most studies was small and in both overall and subgroup analyses; and it is possible that some relevant studies in some localized databases were missed. Secondly, the effect of the confounding ingredients in geneenvironment exposures and lifestyle habits interactions such as environmental factors, and tobacco and alcohol use, were not estimated in the current study due to data available limitation (Table 1). Thirdly, the results were of heterogeneity in some genetic models, possible due to role of various factors such as geographic distribution and racial differences on various predisposing factors involving lifestyle habits. Therefore, to obtain a more accurate results of TP53 codon 72 polymorphism on OPMD onset and progression, additional well-designed studies with larger sample sizes and diverse ethnicities are warranted to validate the associations.

In summary, this is the first pooled-analysis to investigate the association between TP53 codon 72 polymorphism and OPMD onset and progression, suggesting that TP53 polymorphism may not act as genetic factor for the risk of this disease. Combined with the conclusion by a systematic review and meta-analysis [13], we put forward a new opinion that TP53 genetic typing cloud not influence p53 protein expression in OPMD. Further studies are needed to consolidate this opinion.

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s12903-023-03316-0.

Additional file 1: Table S1. Search strategy in literature database.

Additional file 2: Figure S1. Flow diagram of the study selection process. Figure S2. Begg's Funnel plots of association between TP53 codon 72 polymorphism with OPMD onset in (A) allele model, (B) heterozygote model, (C) homozygote model, (D) dominant model, (E) recessive model. Figure S3. Begg's Funnel plots of association between TP53 codon 72 polymorphism with OPMD progression in (A) allele model, (B) heterozygote model, (C) homozygote model, (D) dominant model, (E) recessive model.

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Author' contributions

XY and QZ designed the study. HL, XZ and YL extracted, analyzed, and interpreted the data. HL and YL drafted the manuscript. HL revised the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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