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Polymorphisms of *TP53 Arg72Pro*, but not *p73 G4C14>A4TA4* and *p21 Ser31Arg*, contribute to risk of cutaneous melanoma

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TO THE EDITOR

TP53 responds to diverse stresses, including UVR-induced DNA damage, and regulates many downstream genes to initiate cell-cycle arrest, DNA repair or apoptosis (Kaelin, 1999; Robles and Harris, 2001). *TP53* is the most frequently mutated gene in all forms of human cancers (Hussain and Harris, 1999). In addition to mutations, other genetic events, such as single nucleotide polymorphisms (SNPs) in the *TP53* gene, have been shown to contribute to the development of CM (Han et al., 2006; Stefanaki et al., 2007). The *TP53* gene is located at chromosome 17p13.1 and reportedly has a total of 126 SNPs (http://egp.gs.washington.edu/data/tTP53/tTP53x.csnps.txt). The most frequently studied SNP is a *G*-to-*C* substitution in codon 72, the only known common (*i.e.*, a minor allele frequency > 0.05) non-synonymous (potentially functional) SNP that results in an arginine-to-proline change.

As one of the homologues of TP53, p73 shares a similar molecular structure with TP53 (Jost et al., 1997), playing an important role in carcinogenesis either in the absence of TP53 or independent of TP53 (Kaghad et al., 1997; Wang et al., 2001). Although mutations in *p73* are relatively uncommon, there are two completely linked common SNPs in the non-coding region of exon 2 (4 *G* to *A* and 14 *C* to *T*) that may influence the efficiency of translation initiation and thus may alter cancer risk (Hu et al., 2005; Li et al., 2004). In addition, many other genes are involved in cell-cycle checkpoints, including cyclins, cyclin-dependent kinases (CDK) and

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CDK inhibitors (CDKI). For example, p21 (Waf1/Cip1/CDKN1A) is a CDKI and one of the downstream molecules of TP53. In response to DNA damage, TP53 upregulates p21 expression, leading to either cell-cycle arrest or apoptosis (Xiong et al., 1993). The *p21* gene is located on chromosome 6p21.2, having least 48 SNPs (http://egp.gs.washington.edu/data/cdkn1a/cdk1a.csnps.txt), among which a *C*-to-*A* change in exon 2 is the only common non-synonymous SNP, resulting in a serine-to-arginine change at codon 31 that may have a functional relevance.

Previously, we reported in a relatively small study that the *p53* Arg/Arg genotype was associated with a significantly increased risk of melanoma compared with other genotypes (Shen et al., 2003). To further extend this finding and explore its interaction with variants of other genes, we genotyped for these three functional SNPs (*i.e.*, *TP53 Arg72Pro*, *p73 G4C14>A4T14* and *p21 Ser31Arg*) in 805 non-Hispanic White CM patients and 838 controls frequency matched by age and sex as previously described (Li et al., 2005; Li et al., 2004; Shen et al., 2003). We found that an increased risk of CM was associated with the *TP53 Arg/Arg* genotype (odds ratio = 1.28, 95% confidence interval [CI] 1.05-1.55), compared with the *TP53 Pro/Pro+Arg/Pro* genotype, after adjustment for age and sex, but not with the *p73 G4C14>A4T14* or *p21 Ser31Arg* polymorphisms (Table 1), because variant homozygotes for *p73*and *p21* were relatively uncommon. Further analyses of their combined genotypes revealed some non-significantly elevated CM risk due to reduced sample sizes in the strata (Table 2), although this large study confirmed the association between the *p53* Arg/Arg genotype and increased CM risk (Shen et al., 2003).

The *G*-to-*C* transition at codon 72 in exon 4 resides in a proline-rich region of *TP53* and results in the *Arg* to *Pro* substitution, which is essential for TP53-mediated apoptosis. However, bioinformatics analyses by both sorting intolerant from tolerant and polymorphism phenotyping predict *TP53 Arg72Pro* as a benign change (http://egp.gs.washington.edu/data/tTP53/tTP53x.pph-sift.txt). Our present finding is also consistent with the result of a recently published study of 596 Scottish melanoma patients and 441 population-based controls (Povey et al., 2007), in which the frequency of the *TP53 Arg/Arg* genotype was 57.1% in patients and 53.7% in controls, compared to our result of 57.8% in 805 patients and 51.5% in 838 controls. However, in a Greek study (Stefanaki et al., 2007) of 107 patients with CM and 145 controls and a U.S. Nurses' Health Study (Han et al., 2006) of 219 patients with melanoma and 874 controls, the *Arg* variant genotypes were associated with a non-significantly reduced CM risk. Given the discrepancies in these small studies, larger studies are needed to reconcile these findings.

Little is known about the association between genetic variations of the *p73* gene and risk of CM. Although the exact functional relevance of the *p73 AT* variant allele remains unknown, studies have shown that the *GC to AT* change may lead to the formation of a stem-loop structure that may influence the translation efficacy (Kaghad et al., 1997). Moreover, it was found that 2 N-terminal splice variants of Tap73 (*p73*Δex2 and *p73*Δsx2/3) were increased in melanoma (Tuve et al., 2004). In the present study, our finding of an association between the *AT* homozygous genotypes (*i.e.*, *AT/AT*) and a non-significantly increased risk of CM suggests that either our sample size was not large enough to detect a seemingly small risk, if any, or no risk was associated with the *p73 AT/AT* polymorphism.

As a CDKI, p21 is expected to increase the proliferation of tumor cells when its expression decreases. One study suggested that the loss of p21 may contribute to increased tumorigenic potential in either melanoma cell lines or human melanomas (Mouriaux et al., 1998). Because mutations in the *p21* gene are infrequent in human melanomas (Vidal et al., 1995), we thought genetic variations in *p21* may be an important factor that could modulate the *p21* gene expression, but few studies have investigated the role of *p21* polymorphisms in the etiology

of CM. In a study with only 20 patients and 165 controls (Konishi et al., 2000), *p21 Ser31Arg* variant genotypes were found to be associated with a non-significantly increased risk of CM, which was consistent with our finding in the current, much larger study. The functional relevance of the *p21 Ser31Arg* polymorphism is unknown, and no sorting tolerant from intolerant or polymorphism phenotyping prediction is available. In the present study, the frequency of homozygous *p21* Arg/Arg genotype was too few to be meaningfully evaluated for its association with risk of CM, which warrants larger studies for further validation of our findings.

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This study and research protocol with patient consent and adherence to the Helsinki Guidelines were approved by the M. D. Anderson institutional review board.

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Abbreviations

CDK	cyclin-dependent kinase
CDKI	CDK inhibitor
CI	confidence interval
CM	cutaneous melanoma
OR	odds ratio
PCR	polymerase chain reaction
Polyphen	polymorphism phenotyping
SIFT	sorting intolerant from tolerant
SNP	single nucleotide polymorphism
UVR	ultraviolet radiation

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Table 1

Genotype and allele frequencies of the *TP53 Arg72Pro*, *p73 G4C14>A4T14* and *p21 Ser31Arg* polymorphisms and their associations with risk of CM

Genotype	Patients (n = 805)		Controls (n = 838)[1]		p value[2]	Crude OR (95% CI)	Adjusted OR (95% CI)[3]	Adjusted OR (95% CI)[4]
	N	%	*N*	%				
TP53 Arg72Pro					0.029			
Pro/Pro[5]	40	5.0	56	6.7		1.00	1.00	1.00
Arg/Pro	300	37.2	350	41.8		1.20 (0.77–1.85)	1.20 (0.78–1.86)	1.28 (0.73–2.23)
Arg/Arg	465	57.8	432	51.5		1.51 (0.98–2.31)	1.50 (0.98–2.30)	1.50 (0.87–2.60)
Arg/Pro+Pro/Pro [6]	340	42.2	406	48.5		1.00	1.00	1.00
Arg/Arg	465	57.8	432	51.5		1.28 (1.05–1.55)	1.28 (1.05–1.55)	1.21 (0.95–1.56)
Pro allele frequency	0.236		0.276		0.010			
p73 G4C14>A4T14					0.377			
GC/GC [5]	468	58.1	497	59.3		1.00	1.00	1.00
GC/AT	287	35.7	302	36.0		1.01 (0.82–1.24)	1.01 (0.82–1.24)	1.01 (0.84–1.41)
AT/AT	50	6.2	39	4.7		1.37 (0.88–2.12)	1.37 (0.88–2.12)	1.33 (0.76–2.33)
GC/AT+GC/GC[5]	755	93.8	799	95.4	0.163	1.00	1.00	1.00
AT/AT	50	6.2	39	4.7		1.36 (0.89–2.10)	1.36 (0.89–2.10)	1.29 (0.75-2.24)
AT allele frequency	0.24		0.227		0.401			
p21 Ser31Arg					0.815			
Ser/Ser [5]	695	86.3	731	87.2		1.00	1.00	1.00
Ser/Arg	106	13.2	104	12.4		1.07 (0.80–1.43)	1.06 (0.79–1.41)	1.29 (0.88–1.90)
Arg/Arg	4	0.5	3	0.4		1.40 (0.31–6.28)	1.48 (0.33–6.65)	1.33 (0.18–9.82)
Ser/Arg+Arg/Arg	110	13.7	107	12.8	0.592	1.08 (0.81–1.44)	1.07 (0.80–1.42)	1.30 (0.88–1.89)
Arg allele frequency	0.071		0.066		0.618			

[1] The observed genotype frequency among the control subjects was in agreement with the Hardy-Weinberg equilibrium (Chi-square test = 1.763, p = 0.184 for *TP53 Arg72Pro*; χ^2 = 0.646, p = 0.422 for *p73 G4C14>A4T14*; and χ^2 = 0.118, p = 0.731 for *p21 Ser31Arg)*.

[2] Two-sided χ^2 test for either genotype distribution or allele frequency.

[3] ORs were adjusted for age and sex.

[4]ORs were adjusted for age, sex, skin color eye color, hair color, tanning ability, life time number of sunburns with blistering, freckling in the sun as a child, presence of moles or dyplastic nevi and family history of cancer (cases=700 and controls=513 due to missing data).

[5]Individual comparison reference.

[6]Combine comparison reference.

Table 2

Combined genotype frequencies of the *TP53 Arg72Pro*, *p73 G4C14>A4T14* and *p21 Ser31Arg* polymorphisms and their associations with risk of CM

Combined Genotypes		Patients (*n* = 805)	Controls (*n* = 838)	*p* value[1]	Crude OR (95% CI)	Adjusted OR (95% CI)[2]	Adjusted OR (95% CI)[3]
		N (%)	*N* (%)				
TP53 Arg72Pro	*p21 Ser31Arg*			0.061			
Arg/Pro+Pro/Pro	*Ser/Ser*	287 (35.6)	353 (42.1)		1.00	1.00	1.00
Arg/Arg	*Ser/Ser*	408 (50.7)	378 (45.1)		1.33 (1.08–1.64)	1.32 (1.07–1.63)	1.25 (0.95–1.63)
Arg/Pro+Pro/Pro	*Ser/Arg+Arg/Arg*	53 (6.6)	53 (6.3)		1.23 (0.82–1.86)	1.21 (0.80–1.83)	1.42 (0.83–2.43)
Arg/Arg	*Ser/Arg+Arg/Arg*	57 (7.1)	54 (6.5)		1.30 (0.87–1.94)	1.28 (0.86–1.92)	1.51 (0.88–2.58)
TP53 Arg72Pro	*p73 G4C14>A4T14*			0.089			
Arg/Pro+Pro/Pro	*GC/GC+GC/AT*	317 (39.4)	385 (45.9)		1.00	1.00	1.00
Arg/Arg	*GC/GC+GC/AT*	438 (54.4)	414 (49.4)		1.29 (1.05–1.57)	1.28 (1.05–1.56)	1.22 (0.94–1.57)
Arg/Pro+Pro/Pro	*AT/AT*	23 (2.9)	21 (2.5)		1.33 (0.72–2.45)	1.34 (0.72–2.46)	1.32 (0.59–2.95)
Arg/Arg	*AT/AT*	27 (3.3)	18 (2.2)		1.82 (0.99–3.37)	1.82 (0.99–3.38)	1.56 (0.73–3.32)
p73 G4C14>A4T14	*p21 Ser31Arg*			0.916			
GC/GC+GC/AT	*Ser/Ser*	653 (81.1)	696 (83.0)		1.00	1.00	1.00
GC/GC+GC/AT	*Ser/Arg+Arg/Arg*	102 (12.7)	103 (12.3)		1.06 (0.79–1.42)	1.04 (0.78–1.40)	1.24 (0.84–1.83)
AT/AT	*Ser/Ser*	42 (5.2)	35 (4.2)		1.28 (0.81–2.03)	1.29 (0.81–2.05)	1.17 (0.64–2.12)
AT/AT	*Ser/Arg+Arg/Arg*	8 (1.0)	4 (0.5)		2.13 (0.64–7.11)	2.07 (0.62–6.91)	2.58 (0.63–10.5)

[1]Two-sided chi-square test for distributions of genotypic frequencies between the patients and controls.

[2]ORs were obtained from a multivariate logistic regression model with adjustment for age and sex.

[3]ORs were adjusted for age, sex, skin color eye color, hair color, tanning ability, life time number of sunburns with blistering, freckling in the sun as a child, presence of moles or dyplastic nevi and family history of cancer (cases=700 and controls=513 due to missing data).

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