TP53 codon 72 polymorphism in pigmentary phenotypes

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The p53 protein exerts different cellular functions, and recent findings have demonstrated its influence on the cascade of skin pigmentation during UV exposure. Among *TP53* gene polymorphisms, the most studied is the G to C transversion in exon 4 at codon 72, which results in three distinct genotypes, Arg/Arg, Pro/Pro and Arg/Pro, each one encoding different p53 isoforms. Therefore, this study aimed to determine the relationship between TP53 codon 72 polymorphism and skin protection against sunburn. Genomic DNA was extracted from peripheral blood samples and genotyping was performed by PCR and confirmed by restriction enzyme digestion. The genotype frequency was 50% for Arg/Arg and 14.6% for Pro/Pro genotype. The frequency of heterozygous subjects was 35.4%. In our population, p53 genotypes were in Hardy–Weinberg (HW) equilibrium ($\chi^2_{HM}<3.84$), showing a predominance of arginine allele (total Arg allele frequency of 68%). No significant association between p53 genotype and skin colour, hair or eye colour and susceptibility to sun exposure was found. However, further analysis demonstrated a significant association between the genotype Pro/Pro and blue/green eyes among participants who presented redness ($P=0.016$). Our findings indicate susceptibility to sun exposure when this phenotype (eye colour) occurs simultaneously with Pro/Pro genotype.

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1. Introduction

TP53 is a tumour-suppressor gene (TSG) activated in response to several cellular signals, resulting in the maintenance of genetic stability. Located on chromosome 17, *TP53* gene encodes a 53 kDa protein containing 393 amino acids. Mutations and genetic polymorphisms can alter the function of p53, and when this protein presents polymorphic amino acid sequences, it might lose control of cell division, leading to the initiation, promotion and progression of tumours, or changing other important functions (Ørsted *et al*. 2007; Shu *et al.* 2007). There are 85 validated polymorphisms described for the human TP53 gene that can directly or indirectly influence the metabolic pathways in which it acts (IARC 2011).

The polymorphism at codon 72 in exon 4 encodes two distinct functional allelic forms, arginine (Arg) and proline (Pro), due to a transversion G to C, resulting in different biochemical and biological protein features. As a consequence, three distinct genotypes were created homozygous for arginine (Arg/Arg), homozygous for proline (Pro/Pro) and heterozygous (Arg/Pro). This substitution is in the putative SH3 binding domain of p53, influencing the protein binding capacity and thereby its functional properties (Thomas *et al*. 1999).

A marked difference in biological activity of the two polymorphic forms of p53 was observed. The Pro allele interacts more effectively with elements of the transcriptional machinery then the Arg allele, therefore playing a significant role in inducing G1 cell cycle arrest (Pim and Banks 2004). On the other hand, the Arg allele is significantly more efficient at inducing apoptosis than the Pro allele, presenting a greater ability to localize to the mitochondria and induce cell death (Dumont *et al.* 2003).

More recently, p53 has been shown to influence the tanning response to sunlight by inducing the expression of pro-opiomelanocortin (POMC) gene in human keratinocytes (Cui *et al.* 2007).

Keywords. Polymorphism; p53; pigmentation traits; sunlight susceptibility

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The skin sensitivity to the effects of ultraviolet radiation (UVR) is variable within the normal population, and skin exposure to a significant dose of UVR leads to an inflammatory reaction characterized by erythema (redness), oedema and possibly pain and blistering (sunburn). Although associations between TP53 codon 72 polymorphism and various types of cancer, including skin cancer, were registered (Hsieh and Lin 2006), a few allelic association studies between candidate genes and experimentally induced UVR erythema have been reported (Rees 2004; Benjamin *et al*. 2008; Han *et al.* 2008). The purpose of this study was to establish a possible association between polymorphism at codon 72 of *TP53* gene and pigmentation features such as skin, hair and eye colour as well as skin reactions (redness or tanning) after exposure to sunlight.

2. Materials and methods

2.1 *Subjects*

We randomly selected 96 individuals among the volunteer blood donors of the Instituto de Hematologia Goiano (INGOH), in the municipality of Goiânia, Goiás, Brazil. After the participants signed the informed consent form, 5 mL of blood was collected using disposable material (vacuum blood tubes with ethylenediamine tetraacetic acid as an anticoagulant). They were interviewed by the INGOH staff and were invited to answer a questionnaire. The questionnaire include questions about pigmentation traits such as eye colour (brown/black or blue/green), hair colour (brown/black or bond), skin colour (white, light brown, dark brown or black) and tanning responses using the Fitzpatrick skin type classification (Fitzpatrick 1988). During the interview it was noted that there were inconsistencies regarding the self-declared skin colour. Difficulties in understanding the Fitzpatrick scale were also observed. So the inconsistencies were reported in the Notes section of the questionnaire and the four skin colour categories were grouped into two categories by the authors. The Fitzpatrick scale was replaced by questions about the visible skin reactions (redness or tanning) after a 4 h period of sun exposure (a beach visit, for example). This study was approved by Human and Animal Research Ethics Committee of the Federal University of Goiás (protocol number 125/09).

2.2 *p53 Genotyping*

Genomic DNA was extracted from peripheral blood samples using Illustra™ blood genomic kit, according to the manufacturer's specifications (GE, Healthcare, USA). p53 Pro sequences were detected by PCR using primer pair $Pro^{+}/p53^{-}$ and p53 Arg by the primer pair $p53^{+}/Arg^{-}$ (Storey *et al*. 1998). One-hundred nanograms of template DNA was amplified in a final volume of 50 µL containing 4.5 mmol L^{-1} $MgCl_2$, 200 µmol L^{-1} deoxyribonucleoside triphosphates, 200 nmol L^{-1} primers and 1 U *Taq* polymerase Brasil (Invitrogen, USA). Each set of primers was used in a different tube. After initial denaturation at 94°C for 5 min, samples were amplified for 35 cycles at 94°C for 1 min, 60°C for the Arg allele and 54°C for the Pro allele for 1 min and 72°C for 1 min. Final elongation was at 72°C for 5 min. As negative control, a sample without DNA template was also included in the PCR reaction to ensure that no contamination was introduced. PCR products (141 bp for p53 Arg and 177 bp for p53 Pro) were analysed on a 1.5% agarose gel, stained with ethidium bromide and photographed on a UV light transilluminator.

We confirmed the PCR data by performing restriction fragment length polymorphism (RFLP) analysis using the primer pair $p53^{+}/p53^{-}$ (Storey *et al.* 1998). We amplified the targeted fragment in a 50 µL reaction mixture containing 4.5 mmol L^{-1} $MgCl_2$, 200 µmol L^{-1} deoxyribonucleoside triphosphates, 200 nmol L^{-1} primers and 1 U *Taq* polymerase Brasil (Invitrogen, USA). PCR amplification was performed for 35 cycles consisting of denaturation at 95°C for 30 s, annealing at 58°C for 30 s and extension at 72°C for 45 s. The PCR was preceded by an initiation denaturation step at 94°C for 5 min. The 279 bp fragment was digested by B*st*U I (New England BioLabs, MA, USA) at 60°C according the manufacturer's instructions. The Arg allele has a B*st*U I restriction site resulting in two bands (160–119 bp), and the Pro allele lacks the restriction site. Thus, only Arg/Pro or Arg/Arg were cut, leaving two fragments for the Arg/Arg samples and an additional 279 bp fragment from Pro allele for Arg/Pro heterozygous samples (figure 1). Polymorphisms were detected in a 2% agarose gel stained with ethidium bromide.

2.3 *Statistical analysis*

The Chi square (χ^2) test was used to compare genotype and allele frequencies and characteristics of pigmentation and to assess whether the p53 genotype was in Hardy–Weinberg (HW) equilibrium. A *P*-value of 0.05 was considered significant. The association between TP53 codon 72 polymorphism and pigmentary traits was estimated by calculating the odds ratio (OR) and its 95% confidence interval (CI).

Expected genotype frequencies were calculated from the HW equilibrium:

$$p^2 + 2pq + q^2 = 1,$$

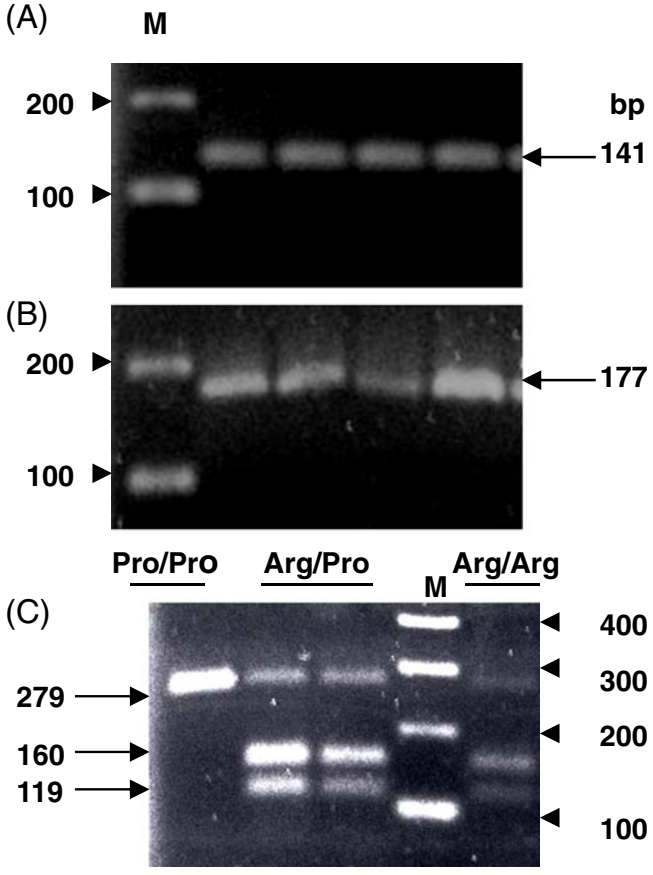

Figure 1. PCR amplification of the TP53 codon 72 sequences. PCR products were electrophoresed through a 2% agarose gel from genomic DNA from (**A**) homozygous arginine (141 bp) or (**B**) homozygous proline (177 bp) subjects. (**C**) PRC products after digestion with B*st*UI: Arg/Arg (160 and 119 bp); Arg/Pro (279, 160 and 119 bp); Pro/Pro (279 bp) genotypes are indicated by arrows. Lane M: 100 bp molecular weight marker (arrowheads).

where p and q were the observed genotype frequencies. Expected and observed genotype were compared as follows:

$$\chi^2_{HW=}(\text{observed Arg/Arg} - \text{expected Arg/Arg})^2/\text{expected Arg/Arg} + (\text{observed Arg/Pro} - \text{expected Arg/Pro})^2/\text{expected Arg/Pro} + (\text{observed Pro/Pro} - \text{expected Pro/Pro})^2/\text{expected Pro/Pro},$$

using a critical value of 3.84 for a degree of freedom (df)=1 (df=number of genotypes minus 1 minus the number of independent values) at the 5% level. All analyses were performed with GraphPad Prism version 4.00 for Windows, GraphPad Software, San Diego California, USA (*www.graphpad.com*).

3. Results

This analysis included 96 blood donors aged between 20 and 70 years. The mean age of subjects was found to be 32 years. Table 1 summarizes the selected characteristics of the subjects. Information regarding skin, hair and eye colour and susceptibility to sun exposure was grouped by the authors. The four skin colour categories (white, light brown, dark brown and black) were grouped into White (white, light brown) and Black/dark brown.

The genotype distribution of the three p53 codon types and frequency of arginine allele are summarized in table 2. In total 48 (50%) had Arg/Arg genotype, while 14 (14.6%) had Pro/Pro genotype. The frequency of heterozygous subjects was 34 (35.4%). In our population, p53 genotypes were in HW equilibrium ($\chi^2_{HM}<3.84$), showing a predominance of arginine allele (total Arg allele frequency of 68%).

We first evaluated the association between the p53 Arg72Pro polymorphism and skin colour. Genotype proportions of different p53 codon 72 gene polymorphisms in both white and black/groups were non-significantly different ($P=0.97$, $\chi^2=0.07$; table 3.). The distributions of Arg/Pro alleles in both groups were 69/31% and 67/33%, respectively, and were also non-significantly different ($P=0.78$, $\chi^2=0.08$; table 3). Therefore, we found no association between TP53 codon 72 polymorphisms and skin colour.

In our sample, 89 (93%) individuals had brown/black hair and 7 (7 %) had blond hair (table 1). The genotypes Arg/Arg, Arg/Pro and Pro/Pro were found in 43 (48.3%), 35 (39.3%) and 11 (12.4%) brown/black-haired individuals,

Table 1. Characteristics of subjects

	Number (n)	%
Age at diagnosis (years)		
≤ 50	90	94
> 50	6	6
Skin colour		
White	37	38.5
Black or dark brown	59	61.5
Eye colour		
Brown/black	85	88
Blue/green	11	12
Hair colour		
Brown/black	89	93
Blond	7	7
Susceptibility to sun exposure[a]		
Redness	36	38.5
Tanning	59	61.5

[a] The numbers do not add up to the total due to missing values.

Table 2. Genotype and Arg allele frequencies of p53 codon 72 polymorphism

Number n (%)				
Arg/Arg	Arg/Pro	Pro/Pro	Arg allele frequency	χ^2_{HW}
			0.68	3.51
48 (50)	34 (35.4)	14 (14.6)		

respectively, and in 4 (55.1%), 1 (14.3%) and 2 (28.6%) blond-haired participants, respectively (table 3). Statistical analysis revealed a non-significant difference in the genotype distributions (P=0.29).

The genotype and allele frequencies were also compared between 85 individuals with brown/black eyes and those with blue/green eyes. There was also no significant difference in the studied frequencies (P=0.89; table 3).

Regarding the frequency of genotypes Arg/Arg, Arg/Pro and Pro/Pro, among the participants who have experienced redness or tanning after exposure to sunlight, the results were 18 (50%), 12 (33.3%) and 6 (16.7%), respectively, for those who had redness, and 30 (51%), 21 (35.6%) and 8 (13.5%), respectively, for those who were tanned (table 3). There was no significant differences in genotype (P=0.91) or allele distribution (P=0.78) between participants who reported have experienced redness or tanning after sunlight exposure (table 3).

Among people with brown/black hair who reported as having experienced redness after sun exposure, the frequencies of genotypes Arg/Arg, Arg/Pro, and Pro/Pro were 14 (43.8%), 13 (40.6%) and 5 (15.6%), respectively; for those who responded that they tanned easily when exposed to sunlight, these frequencies were 29 (51.8%), 20 (35.7%) and 7 (12.5%), respectively (table 4). Analysing the same variables for the individuals presenting blond hair, we observed that the frequencies of genotypes Arg/Arg, Arg/Pro, and Pro/Pro were 3 (75%), 0 (0%) and 1 (25%), whereas for the ones who experienced redness after exposure to sunlight, we registered 1 (33.33%) for each of these genotypes (table 4). So we did not detect association between genotype and redness after sun exposure in participants with brown/black hair, and the same remained true for individuals with blond hair, despite the high odds ratio (OR=6.0, 95% CI=0.22–162.7) for genotype Arg/Arg.

Moreover, 85 participants (88%) had brown/black eyes and 11 (12%) had blue/green eyes (table 1). The frequencies of genotypes Arg/Arg, Arg/Pro and Pro/Pro in individuals with brown/black eyes who reported redness after sun exposure were 15 (50%), 12 (40%) and 3 (10%), respectively, whereas in those who affirmed that they tanned easily when exposed to sunlight, the frequencies were 28 (50.5%), 19 (34.5%) and 8 (14.5%). The same variables were analysed for individuals with blue/green eyes who reported redness after sun exposure and the frequencies of genotypes Arg/Arg, Arg/Pro and Pro/Pro were 2 (33.3%), 1 (16.7%) and 3 (50%), while for those who tanned easily, the frequencies were 2 (50.00%), 2 (50.00%) and 0, respectively (table 4).

We did not detect any association between genotype and redness after sun exposure in participants with brown/black eyes, and the same remained true for individuals with blue/green eyes despite the high odds ratio (OR=9.0, 95% CI=0.34–238.4) for genotype Pro/Pro.

Table 3. Association between the p53 codon 72 polymorphism and pigmentary traits

	Genotype n (%)				Alleles n (%)		
Pigmentary traits	Arg/Arg	Arg/Pro	Pro/Pro	P	Arg	Pro	P
Skin colour				**0.97**			**0.78**
White	19 (51.4)	13 (35.1)	5 (13.5)		51 (69)	23 (31)	
Black/dark brown	29 (49)	21 (36)	9 (15)		79 (67)	39 (33)	
Hair colour				**0.29**			**0.78**
Brown/black	43 (48.3)	35 (39.3)	11 (12.4)		121 (68)	57 (32)	
Blond	4 (55.1)	1 (14.3)	2 (28.6)		9 (64)	5 (36)	
Eye colour				**0.89**			**0.86**
Brown/black	42 (49.4)	32 (37.6)	11 (13)		117 (68)	53 (32)	
Blue/green[b]	5 (45.5)	4 (36.4)	2 (18.1)		14 (64)	8 (36)	
Sun exposure[a]				**0.91**			**0.78**
Redness	18 (50)	12 (33.3)	6 (16.7)		48 (67)	24 (33)	
Tanning	30 (51)	21 (35.5)	8 (13.5)		81 (69)	37 (31)	

[a] The number of participants in this category is not equal to the total number because of missing genotypes.

[b] Three cases had blond hair colour and blue/green eyes.

Table 4. Association between TP53 codon polymorphism and susceptibility to sun exposure according to hair and eye colour

	Redness n (%)	Tanning n (%)	*P*	OR (95% CI)
Brown/black hair				
Arg/Arg	14 (43.8)	29 (51.8)	0.47	0.72 (0.30–1.73)
Arg/Pro	13 (40.6)	20 (35.7)	0.65	1.23 (0.50–3.00)
Pro/Pro	5 (15.6)	7 (12.5)	0.68	1.30 (0.38–4.48)
Blond hair				
Arg/Arg	3 (75)	1 (33.3)	0.27	6.0 (0.22–162.7)
Arg/Pro	0 (0)	1 (33.3)	0.21	0.19 (0.00–6.48)
Pro/Pro	1 (25)	1 (33.3)	0.81	0.67 (0.00–18.07)
Brown/black eye				
Arg/Arg	15 (50)	28 (50.5)	0.94	0.96 (0.04–2.35)
Arg/Pro	12 (40)	19 (34.5)	0.62	1.26 (0.50–3.16)
Pro/Pro	3 (10)	8 (14.5)	0.55	0.65 (0.16–2.67)
Blue/green eye				
Arg/Arg	2 (33.3)	2 (50)	0.60	0.5 (0.04–6.69)
Arg/Pro	1 (16.7)	2 (50)	0.26	0.2 (0.01–3.67)
Pro/Pro	3 (50)	0 (0)	0.09	9.0 (0.34–238.4)

Next, we evaluated the association of the TP53 codon 72 polymorphism and eye colour among participants who experienced redness after sun exposure (table 5). We found a difference in the frequency of Pro/Pro genotype between participants with blue/green and brown/black eyes (P=0.016).

4. Discussion

In this study, we aimed to understand human TP53 codon 72 polymorphism associated with pigmentation characteristics, since this common substitution of one base pair at codon 72 of the gene changes the biochemical and functional properties of the protein. It is now known that these changes alter its role in triggering the cascade of pigmentation by acting as a transcription factor for other genes that are critical in the production of melanin (Pezeshki *et al*. 2006; Cui *et al*. 2007; Nan *et al*. 2008).

Our results showed a predominance of the arginine allele (68%) and the homozygous genotype Arg/Arg represents the most common genotype (50%) among participants. These results are in accordance with a recent study of TP53 polymorphisms among 3794 individuals from a Brazilian population (Thurow *et al*. 2011).

We did not find an association between p53 genotype and skin colour, hair or eye colour and susceptibility to sun exposure. Regarding skin colour, other studies demonstrated that Pro allele occurs at a high frequency in black (>60%) and the Arg allele in white-coloured (>70%) individuals (Själander *et al*. 1996; Sucheston *et al*. 2011). Our results could then be related to the ethnic admixture described in Brazilian population (Ferreira *et al*. 2006). Although we have observed no association between TP53 codon 72 polymorfism and hair or eye colour, to the best our knowledge this is the first time reported for a Brazilian population sample.

Previous studies have demonstrated a borderline association of the Pro/Pro genotype with childhood tanning tendency among black/dark-brown–haired healthy women (Nan *et al*. 2008). We have demonstrated a significant association between the genotype Pro/Pro and blue/green eyes among participants who presented redness. This is an interesting result since redness is related to a high sensitivity to sunlight, although confirmation of these finding would require further studies with a larger number of samples.

Molecular epidemiological studies have explored the association between TP53 codon 72 polymorphism and

Table 5. Association between TP53 codon polymorphism and eye colour among sun-sensitive participants

Genotype	Blue/green n (%)	Brown/black n (%)	*P*	OR (95% CI)
Arg/Arg	2 (33.3)	15 (50)	0.45	0.5 (0.08–3.16)
Arg/Pro	1 (16.7)	12 (40)	0.28	0.3 (0.03–2.90)
Pro/Pro	3 (50)	3 (10)	0.016	9.0 (1.22–66.26)

different types of cancer. An association between allele Arg, skin phototype I-II, burns after exposure to UVR and the development of basal cell carcinoma (BCC) and SCC was reported (McGregor *et al.* 2002; Shen *et al*. 2003; Franchi *et al*. 2006). Also, an association between genotype Arg/Arg in people over 50 years and the risk for cutaneous melanoma was also demonstrated (Stefanaki *et al.* 2007), although an association between allele Pro and the risk for cutaneous melanoma was reported by others (Cui *et al*. 2007; Nan *et al*. 2008).

Additionally, variants of the *TP53* gene seem to confer differential responses to chemotherapy (Sullivan *et al.* 2004). The Arg/Arg phenotype was reported to be associated to a higher response rates and survival in patients with breast (Tommiska *et al.* 2005; Zhuo *et al.* 2009), lung (Nelson *et al.* 2005) or head and neck cancer (Shen *et al.* 2003). However, although a large number of studies evaluating the effect of the p53 codon 72 polymorphism on susceptibility to various cancers have been reported, results are still conflicting, as pointed by Whibley *et al*. (2009).

Usually, when trying to establish some association with genotypic or allelic polymorphism, the disease is already installed and, in most cases, presents an unfavourable prognosis for the patient. However, there is a need to establish the genotypic and allelic frequencies before the development of diseases such as skin cancer, since environmental UV exposure is an early event in skin carcinogenesis, and induces harmful mutations in TP53 gene. Based on these findings, in the near future we may be able to promote prevention campaigns directed to the people's genotypes, since the production of melanin and hence a darker skin, supposedly better protected from sun damage, may camouflage the need for a better protection against exposure to UVR.

5. Conclusions

In this study, no significant association between the TP53 codon 72 polymorphism and skin colour, hair or eye colour and susceptibility to sun exposure was detected at significant levels. The significant association between blue/green eyes and Pro/Pro genotype among the participants presenting redness after sun exposure might raise the risk of developing pigmentation-related diseases.

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References

Benjamin CL, Ullrich SE, Kripke ML and Ananthaswamy H 2008 p53 tumor suppressor gene: a critical molecular target for UV induction and prevention of skin cancer. *Photochem. Protobiol.* **84** 55–62

Cui R, Widlund HR, Feige E, Lin J Y, Wilensky DL, Igras VE, D'Orazio J, Fung CY, *et al.* 2007 Central role of p53 in the suntan response and pathologic hyperpigmentation. *Cell* **128** 853–864

Dumont P, Leu JI, Della Pietra AC, George DL and Myrphy M 2003 The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. *Nat. Genet.* **33** 357–365

Ferreira LB, Mendes-Junior CT, Wiezel CEV, Luizon MR amd Simões AL 2006 Y-STR diversity and ethnic admixture in White and Mulato Brazilian population samples. *Gen. Mol. Biol* **29** 605–607

Fitzpatrick TB 1988 The validity and practically of sun-reactive skin types I through VI. *Arch. Dermatol.* **124** 869–871

Franchi A, Massi D, Gallo O, Santucci M and Porfirio B 2006 Radiation-induced cutaneous carcinoma of the head and neck: is there an early role for p53 mutations? *Clin. Exp. Dermatol.* **31** 793–798

Han J, Kraft P, Nan H, Guo Q, Chen C, Qureshi A, Hankinson SE, Hu FB, *et al.* 2008 A genome-wide association study identifies novel alleles associated with hair color and skin pigmentation. *PLoS Genet.* **4** e1000074

Hsieh YY and Lin CS 2006 p53 Codon 11, 72, and 248 gene polymorphisms in endometriosis. *Int. J. Biol. Sci.* **2** 188–193

IARC (International Agency for Research on Cancer) 2011 Polymorphisms in the TP53 gene *http://www-p53.iarc.fr/polymorphism.html*

McGregor JM, Harwood CA, Brooks L, Fisher SA, Kelly DA, O'nions J, Young AR, Surentheran T, *et al.* 2002 Relationship between p53 codon 72 polymorphism and susceptibility to sunburn and skin cancer. *J. Invest. Dermatol.* **119** 84–90

Nan H, Qureshi AA, Hunter DJ and Han J 2008 Interaction between p53 codon 72 polymorfism and melanocortin 1 receptor variants on suntan response and cutaneous melanoma risk. *Br. J. Dermatol.* **159** 314–321

Nelson HH, Wilkjomen M, Marsit CJ and Keisey KT 2005 TP53 mutation, allelism and survival in non-small cell lung cancer. *Carcinogenesis* **26** 1770–1773

Ørsted DD, Bojesen SE, Tybjaerg-Hansen A and Nordestgaard BG 2007 Tumor supressor p53 Arg72Pro polymorphism and longevity, cancer survival, and risk of cancer in the general population. *J. Exp. Med.* **204** 1295–1301

Pezeshki A, Sari-Aslanl F, Ghaderi A and Doroudchi M 2006 p53 codon 72 polimorphism in basal cell carcinoma of the skin. *Pathol. Oncol. Res.* **12** 29–33

Pim D and Banks L 2004 p53 polymorphic variants at codon 72 exert different effects in cell cycle progression. *Int. J. Cancer* **108** 196–199

Rees JL 2004 The genetics of sun sensitivity in humans. *Am. J. Hum. Genet.* **75** 739–751

Shen H, Liu Z, Strom SS, Spitz MR, Lee JE, Gershenwald JE, Ross MI, Mansfield PF, *et al.* 2003 p53 codon 72 Arg homozygotes are associated with an increased risk of cutaneous melanoma. *J. Invest. Dermatol.* **121** 1510–1514

Shu K, Li B and Wu LX 2007 The p53 network: p53 and its downstream genes. *Colloids Surf. B Biointerfaces* **55** 10–18

Själander A, Birgander R, Saha N, Beckman L and Beckman G 1996 p53 polymorphisms and haplotypes show distinct differences between major ethnic groups. *Human Hered.* **46** 41–48

Stefanaki I, Stratigos AJ, Dimisianos G**,** Nikolaou V, Papadopoulos O, Polydorou D, Gogas H, Tsoutsos D, *et al.* 2007 p53 codon 72 Pro homozygosity increases the risk of cutaneous melanoma in individuals with dark skin complexion and among noncarriers of melanocortin 1 receptor red hair variants. *Br. J. Dermatol.* **156** 357–362

Storey A, Thomas M, Kalita A, Harwood C, Gardiol D, Mantovani F, Judith Breuer, Leigh IM, Matalashewski G and Banks L 1998 Role of a p53 polymorphism in the development of human papilloma-virus-associated cancer. *Nature* **393** 229–234

Sucheston L, Witonsky DB, Hastings D, Yildiz O, Clark VJ, Di Rienzo A and Onel K 2011 Natural selection and functional genetic variation in the p53 pathway. *Hum. Mol. Genet.* **15** 1502–1508

Sullivan A, Syed N, Gasco M, Bergamaschi D, Trigiante G, Attard M, Farrell PJ, Smith P, Lu X and Crook T 2004 Polymorphism in wild-type p53 modulates response to chemotherapy *in vitro* and *in vivo*. *Oncogene* **23** 3328–3337

Thomas M, Kalita A, Labrecque S, Pim D, Banks L and Matlashewki G 1999 Two polymorphic forms of wild type p53 differ biochemically and biologically. *Mol. Cell Biol.* **2** 1092–1100

Thurow HS, Haack R, Hartiwig FP, Oliveira IO, Dellagostin OA, Gigante DP, Horta BL, Collares T and Seixas FK 2011 TP53 gene polymorphism: Importance to câncer, ethnicity and birth weight in a Brazilian cohort. *J. Biosci*. **36** 823–831

Tommiska J, Eerola H, Heinonen M, Salonen L, Kaare M, Tallila J, Ristimäki K, von Smitten K, *et al.* 2005 Breast cancer patients with p53Pro72 homozygous genotype have a poorer survival. *Clin. Cancer Res.* **11** 5098–5103

Whibley C, Pharoah PD and Hollsten M 2009 p53 polymorphisms: cancer implications. *Nat. Rev*. **9** 95–107

Zhuo W, Zhang Y, Xiang Z, Cai L and Chen Z 2009 Polymorphisms of TP53 codon 72 with breast carcinoma risk: evidence from 12226 cases and 10782 controls. *J. Exp. Clin. Cancer Res.* **28** 115

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