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Original article

The genetic association study of TP53 polymorphisms in Saudi obese patients

Jamal S.M. Sabir [a,b,1], Abdelfatteh El Omri [a,b,1], Noor A. Shaik [c,d], Babajan Banaganapalli [c,d], Nahid H. Hajrah [a,b], Houda Zrelli [a,b], Leila Arfaoui [i], Zuhier A. Awan [h], Abdulkader M. Shaikh Omar [e], Arif Mohammed [g], Mona G. Alharbi [a,b], Alawiah M. Alhebshi [a,b], Robert K. Jansen [a,f], Muhummadh Khan [a,b,*]

[a] Center of Excellence in Bionanoscience Research, King Abdulaziz University, Jeddah, Saudi Arabia
[b] Genomics and Biotechnology Section and Research Group, Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia
[c] Department of Genetic Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[d] Princess Al-Jawhara Center of Excellence in Research of Hereditary Disorders, King Abdulaziz Universty, Jeddah, Saudi Arabia
[e] Department of Biology- Zoology Division, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia
[f] Department of Integrative Biology, University of Texas at Austin, Austin, TX 78712, USA
[g] Department of Biology, Faculty of Science, University of Jeddah, Jeddah, Saudi Arabia
[h] Department of Clinical Biochemistry, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[i] Clinical Nutrition Department, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia

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ABSTRACT

Obesity is a multifactorial metabolic disorder characterized by low grade chronic inflammation. Rare and novel mutations in genes which are vital in several key pathways have been reported to alter the energy expenditure which regulates body weight. The *TP53* or *p53* gene plays a prominent role in regulating various metabolic activities such as glycolysis, lipolysis, and glycogen synthesis. Recent genome-wide association studies reported that tumor suppressor gene *p53* variants play a critical role in the predisposition of type 2 diabetes and obesity. Till date, no reports are available from the Arabian population; hence the present study was intended to assess the association between *p53* variants with risk of obesity development in the Saudi population. We have selected three *p53* polymorphisms, rs1642785 (C > G), and rs9894946 (A > G), and rs1042522 (Pro72Arg; C > G) and assessed their association with obesity risk in the Saudi population. Phenotypic and biochemical parameters were also evaluated to check their association with *p53* genotypes and obesity. Genotyping was carried out on 136 obese and 122 normal samples. We observed that there is significantly increased prevalence p52 Pro72Arg (rs1042522) polymorphism in obese persons when compared to controls at GG genotype in overall comparison (OR: 2.169, 95% CI: 1.086-4.334, p = 0.02716). Male obese subjects showed three-fold higher risk at GG genotype (OR: 3.275, 95% CI: 1.230-8.716, p = 0.01560) and two-fold risk at G allele (OR: 1.827, 95% CI: 1.128-2.958, p = 0.01388) of *p53* variant Pro72Arg respectively. This variant has also shown significant influence on cholesterol, LDL level, and random insulin levels in obese subjects ($p \leq 0.05$). In conclusion, *p53* Pro72Arg variant is highly prevalent among obese individuals and may act as a genetic modifier for obesity development among Saudis.

1. Introduction

Obesity is one of the major problem plaguing all over the world today. Obesity is enormously increasing in Saudi Arabia, and it ranks 3rd in the world in obesity. (Al-Hazzaa et al., 2014). The critical factors related to obesity are changes in lifestyle, dietary habits, lack of exercise, and genetic factors. The excessive intake of dietary calories and consumption of less calories leads to the accumulation of fat in different parts of the body. Obesity is recognized as a subclinical inflammatory condition which is linked to

* Corresponding author at: Genomics and Biotechnology Section and Research Group, Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia.
E-mail address: mkmkhan@kau.edu.sa (M. Khan).
[1] Both authors have equally contributed to this article and prefer to be called as "equal first authors"

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many other health disorders. Inflammation associated with obesity adversely affects many tissues and metabolic functions. Compared to healthy individuals obese persons are reported to show a higher level of inflammatory markers such as fibrinogen. Recent studies indicated that hyperinsulinemia is leading to hypertension, type 2 diabetes, arthritis and increased tumor growth (Valentino et al., 2017). They also reported that immune cells such as macrophages and monocytes play a crucial role in obesity-induced inflammation. Along with all these, genetic factors also play a significant role in Obesity. Obesity is also a hereditary disorder. Rare and novel mutations in several key pathways have been reported to alter the energy expenditure rate which regulates body weight. Recent genome-wide association studies reported that tumor suppressor gene *p53* variants are playing a pivotal role in the predisposition of type 2 diabetes and obesity. The *p53* tumor suppressor protein which plays a critical role in cancer progression (Levine et al., 2015). *p53* has been reported to play a crucial role in maintaining innate and adaptive immune mechanisms, reproduction, cell development, neural degeneration, and aging (Hu et al., 2010, Menendez et al., 2013). Previous reports revealed that *p53* protein plays a critical role in metabolism, which is required for its tumor suppressor activity (Kruiswijk et al., 2015, Vousden and Lane, 2007). Moreover, there is substantial evidence that *p53* plays a significant role in metabolic diseases like cardiovascular disease, obesity, and type 2 diabetes (Yahagi et al., 2003, Kruiswijk et al., 2015). Till now more than 200 polymorphic variants have been reported in both exon, promoter and intron regions of the *p53* gene. Numerous studies have reported the risk association of *p53* gene SNPs with cancer, autoimmune thyroid diseases (Chen et al., 2008), systemic lupus erythematosus (Lee et al., 2005), diabetes and other human diseases (Olivier et al., 2010).

The most commonly studied and key *p53* polymorphism occurs at amino acid codon 72, (rs1042522; P72R) is proved to alter the *p53* function. When DNA is damaged *P53* has been reported to promote cell cycle arrest with P72 genotype (Pim and Banks, 2004), and R72 genotype has been proved to enhance apoptosis (Kung et al., 2015). Intron region SNPs rs1642785 which is located on intron-2 of *p53* gene have been reported to enhance cancer risk, and, it also reduces the stability of *p53* pre-mRNA (Perriaud et al., 2014). SNP rs9894946 is shown to have a protective effect on young women with breast cancer. Recent genome-wide association studies revealed a significant association of *p53* variant R72 and increased body mass index (BMI) and type2 diabetes (Kung and Murphy, 2016b). These studies, are supporting that *p53* plays a vital role in developing insulin resistance in mice (Minamino et al., 2009). Molecular interactions of *p53* with two *p53*-regulated genes are TNF and Npc1l1 are possibly responsible for obesity, insulin resistance (Kung et al., 2016a). The association of *p53* polymorphism is linked to many complex diseases in humans, but very few studies are related to obesity. Till date, no reports are available from the Arabian population; hence we were prompted to investigate the association of *p53* gene polymorphisms with the risk of obesity development in the Saudi population.

2. Methods

2.1. Subjects

The study is conducted in accordance to the approval obtained from the local ethics committee on biomedical research. We included 136 unrelated Saudi obese persons and 122 healthy persons from Saudi Arabia. All the participants gave informed consent. Saudi Nationals between 20 and 36 years aged without any health complications were selected for the present study. For each, BMI is calculated following WHO recommendations (Daghestani et al., 2018).

2.2. Biochemical details

Clinical and demographic information such as nationality, age, gender, occupation, education, height, BMI, Waist-to-hip ratio, were measured and recorded. A total of 5 ml of peripheral blood was collected from each participant for biochemical analysis After processing the samples, total cholesterol, triglycerides, HDL level, and LDL levels were estimated using Semi automated Biochemistry Analyzer.

2.3. Genotyping

Genotyping of SNPs in inflammatory genes was performed using TaqMan genotyping assays in obese (n = 136) and normal DNA samples (n = 122). For genotyping experiments, DNA was extracted and diluted to 10 ng/μL for TaqMan genotyping analysis. In the current study, we investigated single nucleotide polymorphisms (SNPs) of the *p53* in Saudi obese patients and healthy individuals. *p53* gene polymorphisms rs1642785 (C > G), rs9894946 (A > G), and rs1042522 (Pro72Arg (C > G) were determined. TaqMan based genotyping analysis was done using the Applied Biosystems 7500 Fast Real-time PCR system as described by (Saadah et al., 2015).

2.4. Statistical analysis

Genotype frequencies were used to calculate Hardy-Weinberg Equilibrium (HWE), Odds ratio (OR), 95% Confidence Interval (CI) and Chi-square ($\chi 2$) results. The T-test was conducted to compare the clinical and biochemical parameters between obese and non-obese groups. The p-value of less than 0.05 was considered to be significant. SPSS statistical package was used for all analysis (SPSS, Chicago, IL, USA). Linkage disequilibrium (LD) plot among the studied SNPs was constructed using Haploview software version 4.2 (Barrett et al., 2004).

3. Results

In the present study, we have assessed the association of *p53* gene polymorphisms with the risk of obesity development. We have included 136 obese (men = 70, women = 66) and 122 normal (men = 68, women = 54) persons for the present study based on anthropometric parameters recommended by WHO. Anthropometric and Biochemical parameters were presented in Table 1 and Table 2 respectively. The mean age of obese subjects was 35.54 ± 7.33, and in non-obese it was 35.22 ± 7.01. There was no significant difference between obese and non-obese in age (p = 0.8) (Table 1). When compared between obese and normal samples except age all the other anthropometric and biochemical parameters showed a significant difference. All the anthropometric parameters such as BMI, waist/hip ratio are significantly higher in obese subjects. Except for HDL, all the other values in biochemical parameters are elevated in obese subjects (Table 2).

We performed the TaqMan allelic discrimination assay, and firstly, we found that no deviations from HWE in both Non-obese and obese samples. A total of 136 obese cases and 122 Non-obese controls were successfully evaluated for genotyping of *p53* SNPs rs1642785, rs9894946, and rs1042522. The genotype frequencies of Non-obese and obese samples are shown in Table 3. All the SNPs are following the Hardy Weinberg equilibrium (P > 0.05).

Table 1
Phenotypic details of non-obese and obese samples.

Variables	Non-obese	Obese	P value
	(n = 122) mean ± SEM	(n = 136) mean ± SEM	
Age (yr)	35.22 ± 7.01	35.54 ± 7.33	0.8
BMI (kg/m^2)	22.21 ± 0.32	35.64 ± 0.57	0.001
Waist (cm)	69.24 ± 0.67	104.46 ± 1.07	0.001
Hip (cm)	95.67 ± 0.73	118.29 ± 1.24	0.001
W/H Ratio	0.71 ± 0.05	0.89 ± 0.04	0.001

Abbreviations: BMI, body mass index; W/H, waist/hip ratio

Table 2
Comparisons of clinical parameters amongst non-obese *vs.* obese study subjects.

Variables	Non-obese (n = 122)	Obese (n = 136)	P value
	mean ± SEM	mean ± SEM	
Cholesterol (mmol/L)	3.43 ± 0.04	4.4 ± 0.07	0.001
Triglyceride (mmol/L)	0.74 ± 0.02	1.302 ± 0.04	0.001
HDL (mmol/L)	1.32 ± 0.03	1.07 ± 0.024	0.001
LDL -cholesterol (mmol/L)	1.55 ± 0.05	2.56 ± 0.06	0.001
Random Insulin (pmol/L)	72.21 ± 2.21	146.03 ± 3.54	0.001
Random Glucose (mmol/L)	5.40 ± 0.041	6.5 ± 0.05	0.001

Abbreviations: HDL: High-density lipoproteins; LDL: Low-density lipoprotein.

The allele and genotype distribution of *p53* SNPs rs1642785, rs9894946 and rs1042522 in non-obese and obese subjects revealed that the *p53* SNP rs1042522 GG (Arg72Arg) genotype was significantly associated with risk when compared to CC (Pro72Pro) genotype (OR: 2.169, 95% CI: 1.086-4.334, p = 0.02716) (Table 3). SNP rs1042522 also showed significant risk at minor allele G (Arg) allele when compared with C allele (OR: 1.501, 95% CI: 1.057-2.130, p = 0.02290). *p53* SNP rs1642785 also showed significant protection at GG genotype (OR: 0.490, 95% CI: 0.239-1.005, p = 0.04986) (Table 3).

The male obese group with GG (Arg/Arg) genotype and minor allele G (Arg) showed an odds ratio of 3.275 (95% CI: 1.230-8.716, p = 0.01560) and 1.827 (95% CI: 1.128-2.958, p = 0.01388), respectively, suggesting that for *p53* rs1042522 GG genotype and G allele was significantly associated with the risk of developing obesity in patients. (Table 4). No significant association was observed with *p53* polymorphisms in female group (Table 5).

Further, we have analyzed the *p53* SNP rs1042522 each genotype (CC, CG, and GG) association separately with phenotypic and biochemical parameters (Table 6). Our results revealed that samples with rs1042522 homozygous genotype (GG (Arg72Arg)) had high BMI, W/H ratio, cholesterol, LDL level, and random insulin levels. Except for HDL level and random glucose, other parameters showed a significant difference at Arg72Arg genotype when compared to Pro72Pro and Pro72Arg (Table 6). There is a significant difference among these parameters when compared with the other two genotype containing samples (Table 6).

3.1. Haplotype analysis

LD plot was constructed to evaluate the additive effect of *p53* polymorphisms on its association with developing obesity, (Fig. 1). Our results revealed that there is a difference in strength among SNPs association in cases and controls. Further we also analyzed the linkage of rs1042522 with other SNPs in other genes using LDProxy tool (https://ldlink.nci.nih.gov/). LDProxy analysis revealed that rs1641549 (D' = 0.9675, r2 = 0.8378), and rs1642785 (D' = 0.9832, r2 = 0.815) SNPs of TP53 gene are showing close association with rs1042522.

4. Discussion

This is the first study to report the association between *p53* gene polymorphism and obesity in the Saudi population. In the present study, a cohort of 136 samples was analyzed for *p53* gene SNPs (rs1642785, rs9894946, and rs1042522) and the relationship with various clinical parameters to check their association with obesity in Saudi Population. The present study showed a strong association with Pro72Arg polymorphism in the Saudi population. We observed that SNP rs1042522 homozygous GG genotype was significantly associated with a two-fold higher risk compared to CC genotype. SNP rs1042522 also showed significant risk at G allele when compared with C allele. Recent next-generation sequencing and GWAS studies revealed that nearly 6 billion people around the world have an Arg72 variant, in which 2.3 billion are homozygous (Consortium 2012). In recent studies, (Burgdorf et al., 2011) and (Gaulton et al., 2008) reported that *p53* has a significant association with type 2 diabetes risk, but the basis of the mechanism was not explained. These studies advocate that *p53* may predispose obesity in people with R72 genotype and this may lead to an enhanced risk to get diabetes. A recent study with a large sample size in Dutch and Finland population reported that there is a strong association among waist circumference and R72 variant (Reiling et al., 2012). (Gloria-Bottini et al., 2011) also reported that *p53* variant Arg72 is associated with increased risk of BMI and diabetes. The previous reports are inconsistent with our observations that samples Arg72 variant plays a crucial role in developing obesity by increasing the BMI, W/H ratio, cholesterol,

Table 3
Genotype frequencies of *p53* gene polymorphism in obese and non-obese study participants.

SNP	Variant	Obese	Non-obese	OR	CI	χ^2 Value	P- Value
rs1642785	CC	49 (0.36)	40 (0.33)	Ref			
	CG	69 (0.51)	52 (0.44)	1.083	0.624–1.880	0.08	0.77631
	GG	18 (0.13)	30 (0.23)	0.490	0.239–1.005	3.85	0.04986
	C	167(0.61)	132(0.54)	Ref			
	G	105(0.39)	112(0.46)	0.741	0.522–1.052	2.81	0.09358
rs9894946	AA	71 (0.52)	65(0.53)	Ref			
	AG	50(0.37)	49(0.40)	0.934	0.556–1.568	0.07	0.79672
	GG	15(0.11)	8(0.07)	1.717	0.683–4.315	1.34	0.24682
	A	192(0.71)	179(0.73)	Ref			
	G	80(0.29)	65(0.27)	1.147	0.780–1.687	0.49	0.48423
rs1042522	CC	39(0.29)	47(0.39)	Ref			
	CG	61(0.45)	55(0.45)	1.337	0.764–2.339	1.03	0.30903
	GG	36(0.26)	20(0.16)	2.169	1.086–4.334	4.88	0.02716
	C	139(0.51)	149(0.61)	Ref			
	G	133(0.49)	95(0.39)	1.501	1.057–2.130	5.18	0.02290

Table 4
Genotype frequencies of p53 gene polymorphism in male obese and non-obese study participants.

SNP	Variant	Obese	Non-obese	OR	CI	χ^2 Value	P- Value
rs1642785	CC	25(0.36)	21(0.31)	Ref			
	CG	37(0.53)	29(0.43)	1.072	0.503–2.285	0.03	0.85764
	GG	8(0.11)	18(0.26)	0.373	0.135–1.030	3.72	0.05377
	C	87(0.62)	71(0.52)	Ref			
	G	53(0.38)	65(0.48)	0.665	0.412–1.075	2.78	0.09526
rs9894946	AA	37(0.52)	31(0.46)	Ref			
	AG	24(0.37)	32(0.47)	0.628	0.308–1.281	1.64	0.20027
	GG	9(0.11)	5(0.07)	1.508	0.457–4.971	0.46	0.49781
	A	98(0.71)	94(0.69)	Ref			
	G	42(0.29)	42(0.31)	0.959	0.574–1.602	0.03	0.87345
rs1042522	CC	19(0.27)	28(0.41)	Ref			
	CG	31(0.44)	31(0.46)	1.474	0.685–3.171	0.99	0.32047
	GG	20(0.29)	9(0.13)	3.275	1.230–8.716	5.85	0.01560
	C	69(0.49)	87(0.64)	Ref			
	G	71(0.51)	49(0.36)	1.827	1.128–2.958	6.05	0.01388

Table 5
Genotype frequencies of p53 gene polymorphism in female obese and non-obese study participants.

SNP	Variant	Obese	Non-obese	OR	CI	χ^2 Value	P- Value
rs1642785	CC	24(0.35)	19(0.35)	Ref			
	CG	32(0.43)	23(0.43)	1.101	0.492–2.466	0.06	0.81417
	GG	10(0.22)	12(0.22)	0.660	0.235–1.853	0.63	0.42879
	C	80(0.56)	61(0.56)	Ref			
	G	52(0.44)	47(0.44)	0.844	0.503–1.414	0.42	0.51845
rs9894946	AA	34(0.52)	34(0.63)	Ref			
	AG	26(0.39)	17(0.31)	1.529	0.705–3.318	1.16	0.28113
	GG	6(0.09)	3(0.07)	2	0.462–8.656	0.88	0.34698
	A	94(0.71)	85(0.79)	Ref			
	G	38(0.29)	23(0.21)	1.494	0.824–2.709	1.76	0.18480
rs1042522	CC	20(0.30)	19(0.35)	Ref			
	CG	30(0.45)	24(0.44)	1.188	0.520–2.713	0.17	0.68336
	GG	16(0.24)	11(0.20)	1.382	0.513–3.725	0.41	0.52223
	C	70(0.53)	62(0.57)	Ref			
	G	62(0.47)	46(0.43)	1.194	0.715–1.992	0.46	0.49771

Table 6
Phenotypic and Biochemical Characteristics of samples clustered according to rs1042522 (Pro72Arg).

Phenotypic variables	Pro72Pro	Pro72Arg	Arg72Arg	P-value
	(n = 86) mean ± SE	(n = 116) mean ± SE	(n = 56) mean ± SE	
BMI (kg/m^2)	28.4 ± 0.35	33.47 ± 4.28	43.7 ± 2.1	0.001
Waist(cm)	84.54 ± 1.64	99.03 ± 1.97	117.23 ± 3.54	0.001
Hip(cm)	107.54 ± 0.67	111.54 ± 2.67	130.24 ± 3.24	0.001
W/H ratio	0.79 ± 0.01	0.86 ± 0.01	0.93 ± 0.03	0.001
Cholesterol (mmol/L)	4.01 ± 0.04	4.67 ± 0.12	5.87 ± 0.41	0.001
Triglyceride (mmol/L)	1.07 ± 0.02	1.34 ± 0.06	1.71 ± 0.15	0.001
HDL (mmol/L)	1.21 ± 0.03	1.14 ± 0.03	1.06 ± 0.14	0.335
LDL (mmol/L)	2.12 ± 0.021	2.41 ± 0.13	3.45 ± 0.16	0.001
Random Insulin (pmol/L)	84.21 ± 2.54	133.24 ± 4.65	148 ± 9.54	0.001
Random Glucose(mmol/L)	5.41 ± 0.021	6.01 ± 0.09	6.75 ± 0.06	0.05

LDL level, and insulin levels. (Molchadsky et al., 2013) reported that *p53* confer protection against diet-induced obesity by enhancing the oxidation of brown fat. (Kung et al. 2016a) demonstrated that mice with *p53* Arg72 variant developed obesity when fed with a high-fat diet. They also reported that mice with R72variant developed insulin resistance and fatty liver disease. In gene expression studies Kung et al. reported that Tnf and Npc1l1 genes are associated with the *p53* R72 variant in obesity development.

In the present study, we also sub-analyzed the possible association between three *p53* SNPs and their association with obesity based on gender. In the gender comparison, SNP rs1042522 was associated with a significant risk of obesity in males when compared to females. These results are inconsistence with a previous study conducted in the Brazilian population, in which they reported that women conferred significant risk to develop obesity with SNP rs1042522 (Smith et al., 2007).

In the present study, *p53* Arg72 genotype samples showed lower HDL levels when compared with other genotypes; a similar pattern was also reported in the European population (Smith et al. 2007). The exact mechanism between a low level of HDL and *p53* is not known, but this may lead to other health complications such as cardiovascular problems. By regulating glycolysis and citric acid cycle wild-type, *p53* is controlling lipid metabolism (Berkers et al., 2013). Mutations in *p53* may interrupt the fatty acid oxidation function (Jiang et al. 2011, Maddocks and Vousden 2011). *p53* SNP rs1642785 also showed significant protection at GG genotype with a borderline significance. rs1642785 located on intron-2 of *p53* gene has been reported to reduce the stability of *p53* pre-

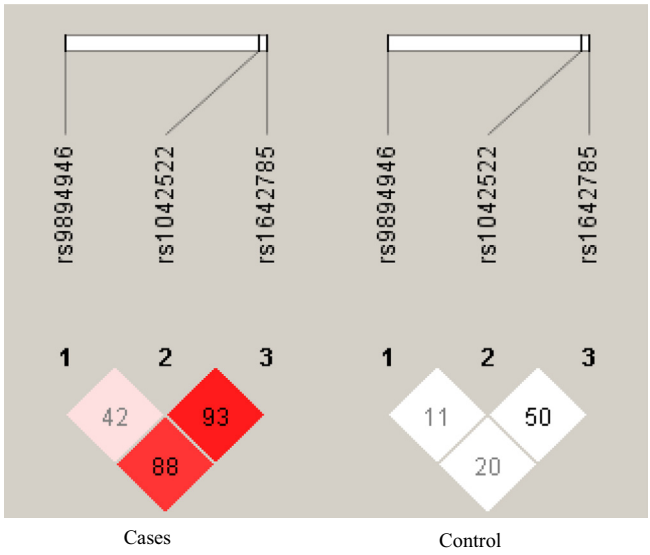

Fig. 1. Pairwise LD among the 3 SNPs in colon cancer and controls. The thick red color indicates the higher D'.

mRNA (Perriaud et al., 2014). Although it showed a low level of significance, its relative frequency is higher in cases than in controls. The mutant allele can affect the transcription levels of *p53*, as it is located in the CA-rich region which plays a key role in inducing destabilization of *p53* mRNAs. One more SNP studied rs9894946 was also didn't showed any association with obesity. Linkage disequilibrium analysis revealed that there is a difference in strength among SNPs association in cases and controls. Two of the SNPs rs1042522 (D' = 0.93) and rs1642785 (D' = 0.88) showed higher D' values in obese subjects compared to non-obese subjects.

SNP rs1042522 is a non-synonymous mutation, which replacing the Proline amino acid with Arginine at 72 amino acid position. The wild-type amino acid is comparatively small in size than the mutant. The charge introduced by mutant amino acid can cause repulsion with neighboring amino acids. Proline to Arginine change may lead to loss of hydrophobic interactions with other amino acids. At this position replacement of Arginine at this position might disturb the protein backbone confirmation.

In conclusion, our study suggests that the *p53* gene SNP rs1042522 (Pro72Arg) modulate the risk of obesity in the Saudi population. Analysis of *p53* variants in normal subjects might help to identify obesity risk, which allows taking precautionary measures like changing food habits. This is the first study demonstrating the association between *p53* polymorphisms and obesity risk in the Arabian population. Further research is required in a large cohort to confirm our findings.

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