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Investigating the Association of Poly (ADP-Ribose) Polymerase-1 (PARP-1) and Nuclear Factor-κB (NF-κB) Polymorphisms with Vitiligo Susceptibility

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ABSTRACT

Background: Poly (ADP-ribose) polymerase-1 (PARP-1) is a co-activator of nuclear factor-κB (NF-κB) and is also strongly activated by DNA damage. PARP has also been found to be associated with several autoimmune disorders. Vitiligo is a polygenic, multifactorial, acquired skin disorder caused due to loss of epidermal melanocytes. Among others, genetic and immunological factors are associated with vitiligo pathogenesis.
Aim: To investigate the association of PARP1 exon 17 (rs1136410; V762A) and promoter CA microsatellite repeat (rs1136410) polymorphisms, and NF-κB promoter -94 indelATTG (rs28362491) polymorphism with vitiligo pathogenesis in Gujarat population.
Methods: Genotyping of *PARP1* 17T/C (rs5030870) polymorphism was done by PCR-RFLP.*PARP1* CA microsatellite and *NF-κB*-94 indel (rs28362491) polymorphisms were genotyped by Real-Time PCR. Anti-PARP antibody levels were assessed by ELISA.
Results: The results suggested no significant difference in allele and genotype frequencies of *PARP1* 17 T/C (p=0.5094 and p=0.4201, respectively), *PARP1* CA microsatellite polymorphisms (p=0.9519 and p=0.9338, respectively) and N*F-κB*-94 ATTG indel polymorphism (p=0.1482 and p=0.3784, respectively) in patients as compared to controls.
Conclusion: This study suggests no association of PARP1 17 T/C, PARP1 CA microsatellite and NF-κB-94 ATTG indel polymorphisms with vitiligo susceptibility in Gujarat population. Additionally, anti-PARP1 antibody levels were not significantly different among patients and controls. These findings suggest the need for additional studies to explore the role of PARP1 in vitiligo pathogenesis.

Keywords: Vitiligo, poly (ADP-ribose) polymerase-1(PARP-1), nuclear factor-κB (NF-κB), polymorphisms, Autoimmunity

1. INTRODUCTION

Vitiligo is a known, acquired skin disfiguring disease characterized by white colored patches due to loss of functional melanocytes from the skin. A study on vitiligo metanalysis reported 0.2-1.8% worldwide prevalence of vitiligo from population and hospital based studies [1]. Several theories are put forward to explain the aetiology of the disease, such as autoimmune, oxidative stress, genetic and neural hypotheses [2-4]. The complex interaction between immunological, environmental, biochemical and genetic factors collectively generates a tolerant sphere [5]. The complex genetics of vitiligo includes multiple susceptibility loci, incomplete penetrance and genetic

heterogeneitywith gene-gene and gene-environment interactions [6]. Till now, approximately 50 vitiligo susceptible loci have been reported as risk factors for vitiligo using the GWAS approach, from which a significant fraction of genes are involved in immune regulation and others play a role in melanocyte regulation and cellular apoptosis [7]. Genetic polymorphisms possibly predispose the patients to autoimmune dysregulation and melanocyte abnormalities.

Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear enzyme activated by DNA damage and implicated in many essential cellular processes, including gene transcription, DNA damage, genomic stability, autoimmunity, metabolism and apoptosis [8-10]. The human *PARP1* gene consists of 23 exons spanning 43 kb and contains a polymorphic CA nucleotide repeat in the 5' flanking sequence [11]. The long microsatellite (CA)n repeats facilitate the formation of DNA racket structures in the promoter region that bring the TATA boxes into the vicinity of the transcription factor binding site [12]. This (CA)n microsatellite is located close to the binding site of the transcription factor Yin Yang 1(YY1) and thereby regulates *PARP1* expression[13]. Another active site polymorphism of *PARP1* is T2444C (rs1136410; Val762Ala) [14], which was suggested to reduce the PARP1 enzymatic activity by ~40 %[15-18].

PARP1 also acts as a co-activator of nuclear factor-κB (NF-κB) and regulates NF-κB dependent gene expression, which mediates varied transcriptional programs [19]. NF-κB regulates the transcription of several genes for cell adhesion, immune response, differentiation, cytokine and chemokine production, proliferation, apoptosis and angiogenesis [20]. Abnormalities in the NF-κB regulation are involved in multiple human pathologies, including immune deficiencies, inflammatory diseases, diabetes, atherosclerosis and tumors [21-23]. NF-κB1 gene contains an insertion/deletion (indel) polymorphism (ATTG) at 94 site of the promoter [24].The ATTG insertion in NF-κB1 promoter has been proposed to increase promoter activity [25].

In the present study, we have investigated the association of PARP1 exon 17 (rs1136410; V762A) and promoter CA microsatellite repeat polymorphisms and NF-κB -94 indel ATTG (rs28362491) polymorphism in Gujarat vitiligo patients and controls along with serum anti-PARP antibody levels.

2. MATERIALS AND METHODS

2.1. Study subjects

A total of 149 vitiligo patients and 152 healthy age and gender matched controls were recruited for blood samples. Demographic particulars for the study subjects are provided in the supplementary table S1. Diagnosis of disease and inclusion-exclusion criteria was followed as described earlier [34]. The importance of our study was explained to all participants, and written consent was obtained from all study subjects.

2.2. Ethics statement

The study plan was approved by the Institutional Ethics Committee for Human Research, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India (FS/IECHR/BC/RB/1).

2.3. Genomic DNA preparation

2 ml venous blood was collected from the patients and healthy subjects in K_3EDTA coated vacutainers (BD, Franklin Lakes, USA). Genomic DNA was extracted from whole blood using QIAamp DNA Blood Kit (QIAGEN Inc., Valencia, USA) according to the manufacturer's instructions. After extraction, concentration and purity of DNA was determined spectrophotometrically, quality of DNA was also determined on 0.8% agarose gel electrophoresis and DNA was stored at -20º C until further analyses.

2.4. Genotyping of *PARP1* exon 17 T/C (rs1136410) single nucleotide polymorphism

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to genotype exon 17 T/C (rs1136410) polymorphism of *PARP1* in 152 controls and 149 patients (Fig. S1A). The primers used for genotyping are shown in Table S2. The reaction mixture of the total volume of 20 μL included 5 μL (100 ng) of genomic DNA, 10 μL nuclease-free H_2O, 2.0 μL 10x PCR buffer, 2 μL 2 mMdNTPs (SIGMA Chemical Co, St. Louis, Missouri, USA), 0.3 μL of 10 μM corresponding forward and reverse primers (Eurofins, Bangalore, India), and 0.3 μL (5U/μL) Taq Polymerase (Bangalore Genei, Bangalore, India). Amplification was performed using an Eppendorf Master cycler gradient according to the protocol: 95ºC for 10 min followed by 35 cycles of 95ºC for 30 s, primer dependent annealing (Table S2) for 30 s, and 72ºC for 30 s. The amplified products were checked by electrophoresis on a 2% agarose gel stained with ethidium bromide. Restriction enzyme *Aci*I (Fermentas, Lithuania) was used for digestion of PCR amplicons of PARP1 for genotyping of exon 17 T/C (rs1136410) (Table S2). 15 μL of the amplified products were digested with 1U of the restriction enzyme in a total reaction volume of 20 μL as per the manufacturer's instruction. The digested products with 50 bp DNA ladder (Bioron, Ludwigshafen am Rhein, Germany) were resolved on 3.5% agarose stained with ethidium bromide and visualized under UV transilluminator. More than 10% of the samples were randomly selected for confirmation, and the results were 100% concordant (analysis of the chosen samples was repeated by two researchers independently).

Table 1: Distribution of genotype and allele frequencies for *PARP1* exon 17T/C *(*rs1136410) SNP in Gujarat Vitiligo patients and controls

Samples	Observed Genotype frequency			Observed Allele frequency		Expected genotype frequency			
	TT	CT	CC	T	C	TT	TC	CC	*p* (HWE)[a]
Control (n=152)	129	23	-	281	23	129.87	21.26	0.87	0.3129
Patients (n=149)	122	27	-	270	28	122.32	25.37	1.32	0.7615
p-value OR (CI 95%)	0.5094[b]			0.4201[c] 1.267 (0.7119-2.255)					

a Observed vs. expected according to the Hardy-Weinberg equation.
b Controls vs. patients using the chi-square test with 3 × 2 contingency table.
c Controls vs. patients using the chi-square test with 2 × 2 contingency table.

2.5. Genotyping of CA microsatellite of *PARP1* by high-resolution melt (HRM) curve analysis

PARP1 CA microsatellite was genotyped by High-ResolutionMelt (HRM) curve análisis using LightCycler® 480 Real-Time PCR protocol in 139 controls and 134 patients. Real-time PCR was performed in 20 μl volume using LightCycler®480 HRM Master mix (Roche Diagnostics GmbH, Mannheim, Germany) following the manufacturer's instructions and carried out in the Light Cycler 480 Real-Time PCR (Roche Diagnostics GmbH, Mannheim, Germany). The thermal cycling conditions included an initial activation step at 95ºC for 10 min, followed by 45 cycles of denaturation, annealing, and amplification (95ºC for 15 s, primer dependent annealing for 20 s, 72ºC for 20 s). The fluorescence

signals were collected at the extension step. At the end of the amplification phase, a high-resolution melting curve analysis was carried out on the product formed as per the manufacturer's instructions. Based on the HRM curve, all the samples were grouped into five categories (Supplementary fig. S2B). Selected samples from each of these groups were sequenced using the primer set 2 (Supplementary Table S2), and the number of CA repeats was determined (Supplementary fig. S2B). The samples grouped according to the length of the repeat under three genotypes as: SS: (CA)10-12 / (CA)10-12; SL: (CA)10-12 / (CA)13-16; LL: (CA)13-16 / (CA)13-16.

Table 2: Distribution of genotype and allele frequencies for *PARP1* CA microsatellite repeat polymorphism in Gujarat Vitiligo patients and controls

SNP	Genotype and allele	Controls (frequency)	Vitiligo patients (frequency)
PARP CA repeats	**Genotype**	**(n = 139)**	**(n = 134)**
	CA 10-12	29 (0.21)	29 (0.22)
	CA 10-13	13 (0.09)	14 (0.10)
	CA 11-11	00 (0.00)	03 (0.02)
	CA 12-12	21 (0.15)	15 (0.11)
	CA 16-16	76 (0.55)	73 (0.55)
	Allele		
	CA 10	42 (0.15)	43 (0.16)
	CA 11	00 (0.00)	6 (0.022)
	CA 12	71 (0.25)	59 (0.22)
	CA 13	13 (0.05)	14 (0.05)
	CA 16	152 (0.55)	146 (0.55)

The samples grouped according to the length of the repeat under three genotypes: - SS: (CA) 10-12 / (CA) 10-12; SL: (CA) 10-12 / (CA) 13-16; LL: (CA) 13-16 / (CA) 13-16

2.6. Genotyping of NF-κB -94 indel (rs28362491; ATTG) by high-resolution melt (HRM) curve analysis

NF-κB–94 indel (rs28362491; ATTG) was genotyped by High-ResolutionMelt (HRM) curve análisis using LightCycler® 480 Real-Time PCR protocol in 140 control and 131 patients from the Gujarat population. Real-time PCR was performed in 20 µl volume using LightCycler®480 HRM Master (Roche Diagnostics GmbH, Mannheim, Germany) following the manufacturer's instructions and carried out in the Light Cycler 480 Real-Time PCR (Roche Diagnostics GmbH, Mannheim, Germany). The thermal cycling conditions included an initial activation step at 95ºC for 10 min, followed by 45 cycles of denaturation, annealing, and amplification (95ºC for 15 s, primer dependent annealing for 20 s, 72ºC for 20 s). The fluorescence data collection was performed during the extension step. At the end of the amplification phase, a high-resolution melting curve analysis was carried out on the product formed as per the manufacturer's instructions. Based on the HRM curve, all the samples were grouped into three categories, i.e., II (homozygous insertion), ID (heterozygous), DD (homozygous deletion) (Supplementary fig. S3B).

2.7. Estimation of Anti-PARP1 antibodies in vitiligo patients

Anti-PARP antibodies were estimated in sera of 140 vitiligo patients and 54 controls by ELISA (Calbiochem, Gibbstown, NJ, USA).

2.8. Statistical analyses

Evaluation of the Hardy-Weinberg equilibrium (HWE) was performed for all three polymorphisms in patients and controls by comparing the observed and expected frequencies of the genotypes using chi-squared analysis. The distribution of the genotypes and allele frequencies of *PARP1* and *NF-kB* polymorphisms for patients and control subjects was compared using chi-squared test with 3×2 and 2×2 contingency tables using Prism 6 software (GraphPad Software Inc; San Diego CA, USA, 2003). The odds ratio (OR) with a respective

confidence interval (95% CI) for disease susceptibility was also calculated.

3. RESULTS

3.1. Analysis of association between *PARP1* exon 17 (rs1136410; T/C) and promoter CA microsatellite polymorphisms and susceptibility to vitiligo

For *PARP1* T/C SNP, two genotypes were identified in both patients and controls, i.e., TT and TC, whereas homozygous CC genotype was absent (Supplementary fig. S1). However, there was no significant difference observed between genotype and allele frequencies for the *PARP1* T/C polymorphism (p=0.5094 and p=0.4201 respectively; Table 1), suggesting *PARP1*exon 17 T/C (rs1136410) is not associated with vitiligo susceptibility. Both control and patient groups were in HWE (p=0.3129 and p=0.7615, respectively).

For *PARP1* CA microsatellite repeat polymorphism, the samples were grouped according to the length of the repeat under three genotypes: - SS: (CA) 10-12 / (CA) 10-12; SL: (CA) 10-12 / (CA) 13-16; LL: (CA) 13-16 / (CA) 13-16 (Supplementary fig. S2; Table 2). However, no significant difference was found for genotype and allele frequencies between controls and patients (p=0.9519 and p=0.9338 respectively; Table 3), suggesting *PARP1*promoter CA polymorphism is not associated with vitiligo susceptibility.

Table 3: Distribution of Genotype and Allele frequencies for *PARP1* CA microsatellite repeat polymorphism in Gujarat Vitiligo patients and controls

Sample	Observed Genotype frequency			Observed Allele frequency		Expected genotype frequency			
	SS	SL	LL	S	L	SS	SL	LL	*p* (HWE)[a]
Control (n=139)	50	13	76	113 (0.41)	165 (0.59)	22.97	67.07	48.97	<0.0001
Patients (n=134)	47	14	73	108 (0.40)	160 (0.60)	21.76	64.48	47.76	<0.0001
p-value OR (CI 95%)	0.9519b			0.9338[c] 1.015 (0.7208 to 1.428)					

a Observed vs. expected according to the Hardy-Weinberg equation.
b Controls vs. patients using the chi-square test with 3 × 2 contingency table.
c Controls vs. patients using the chi-square test with 2 × 2 contingency table.

3.2. Analysis of association between *NF-κB* -94 indel(rs28362491; ATTG) and susceptibility to vitiligo

Genotyping of *NF-κB*-94 indel polymorphism was performed in 140 controls and 131 patients from the Gujarat population using the HRM technique. Based on the HRM curve, all the samples were grouped into three categories, i.e., II (homozygous insertion), ID (heterozygous indel), DD (homozygous deletion) (Supplementary fig. S3). No significant difference was found in genotype and allele frequencies between controls and patients (p=0.1482 and p=0.3784, respectively; Table 4), suggesting *NF-κB*-94 ATTG indel promoter polymorphism is not associated with vitiligo susceptibility. The control group was in HWE, whereas the vitiligo patient group deviated from HWE (p=0.1171 and p=0.0002, respectively).

Table 4: Distribution of genotype and allele frequencies for *NFκB*-94 ATTG Indel promoter polymorphism in Gujarat vitiligo patients and controls.

Sample	Observed Genotype frequency			Observed Allele frequency		Expected genotype frequency			
	II	ID	DD	I	D	II	ID	DD	*p*(HWE)[a]
Control (n=140)	21	55	64	93 (0.35)	183 (0.65)	16.8	63.4	59.8	0.1171
Patients (n=131)	21	37	73	79 (0.3)	183 (0.70)	11.9 1	55.18	63.91	0.0002
p-value OR (CI 95%)	0.1482[b]			0.3784[c] 1.177 (.8186 to 1.693)					

a Observed vs. expected according to the Hardy-Weinberg equation.
b Controls vs. patients using the chi-square test with 3 × 2 contingency table.
c Controls vs. patients using the chi-square test with 2 × 2 contingency table.

3.3. Anti-PARP antibody levels in vitiligo patients

The levels of anti-PARP antibodies were estimated in the sera of 140 vitiligo patients and 54 controls. No significant difference was found in anti-PARP antibody levels between patients and controls (*p*= 0.9177; Fig. 1).

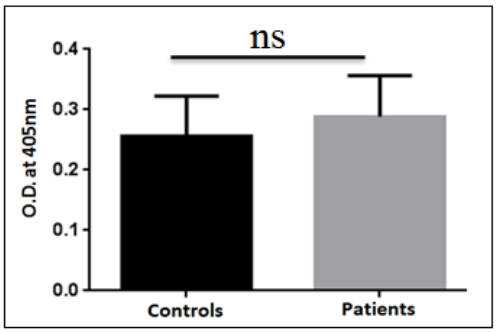

Figure 1: The anti-PARP antibody levels were estimated in sera of 140 vitiligo patients and 54 controls. There was a non-significant (ns) difference in anti-PARP antibody levels between vitiligo patients and controls (*p*= 0.9177).

4. DISCUSSION

Vitiligo is a multifactorial polygenic depigmentation disorder characterized by loss of functional melanocytes [26]. Vitiligo is conjectured to be of autoimmune origin, with the involvement of genetic factors in precipitating depigmentation in genetically susceptible individuals.

PARP-1 is a key enzyme that regulates DNA repair, immune functions and gene transcription. PARP1 catalyzes the poly(ADP-ribosyl)ation of proteins, including itself using NAD+ as a substrate. The PARP's DNA binding domain contains the Zinc Fingers that recognize single and double-stranded breaks, and PARP-1 forms homodimers and catalyzes the cleavage of NAD+ into the ADP-ribose and nicotinamide [8-10,20]. It has been suggested that the variant CC homozygote in *PARP1* T/C exon 17 (Val762Ala) polymorphism causes about a 40% decrease in PARP1 activity [7] and is common in Caucasian and Asian populations. The frequency of minor allele homozygote (CC) was shown to be associated with an increased risk for prostate cancer in Europeans [27], or lung cancer and

esophageal cancers in Chinese heavy smokers [28,29]. The other *PARP1* promoter CA microsatellite repeat polymorphism is located in close proximity to the binding site of transcription factor YY1, and the length of the repeat might be spatially important for its interactions with other transcription factors [13]. Previous studies showed that a long CA microsatellite is related to autoimmune diseases such as rheumatoid arthritis and coeliac disease [30,31]. The above studies implicate the involvement of PARP1 in inflammatory processes leading to the development of immunological disorders. Though we studied two polymorphisms of *PARP1*: exon 17 (rs1136410; V762A) and promoter CA microsatellite repeat in Gujarat vitiligo patients and controls, we did not find the association of both of these polymorphisms with vitiligo susceptibility (Supplementary fig. S2). Our recent study suggests that PARP-1 plays a critical role in oxidative stress-mediated melanocyte death, hence is also involved in vitiligo pathogenesis [32]. Also, PARP1 is found to modulate the transcription of genes whose products regulate the inflammatory response. Thus, PARP1 regulates nuclear factor-κB (NF-κB) dependent transcription and synthesis of inflammatory mediators, i.e., IL-1, IL-6, TNF-α and inducible nitric oxide (NO) synthase [33], which are key elements in the pathophysiology of inflammation and cell death. Therefore, we also investigated the NF-κB-94 indel(rs28362491; ATTG) polymorphism. However, it was also not found to be associated with vitiligo susceptibility (Supplementary fig. S3).

5. CONCLUSION

In conclusion, the present study suggests that the *PARP1*exon 17 T/C (rs1136410) and PARP1 promoter CA polymorphisms are not associated with vitiligo susceptibility. Also, NF-κB-94 ATTG indel promoter polymorphism is not associated with vitiligo susceptibility. Anti-PARP1 antibody levels in sera of vitiligo patients were also not significantly different from controls. Additional studies are warranted to explore the role of PARP1 and NF-κB in vitiligo pathogenesis.

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Conflict of Interest: None

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