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Journal of Asthma

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597262>

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Online Publication Date: 01 May 2009

To cite this Article Tezcan, Gulçin, Gurel, Cigdem Bayram, Tutluoglu, Bulent, Onaran, Ihan and Kanigur-Sultuybek, Gonul(2009)'The Ala Allele at Val762Ala Polymorphism in Poly(ADP-ribose) Polymerase-1 (PARP-1) Gene is Associated with a Decreased Risk of Asthma in a Turkish Population', Journal of Asthma, 46:4, 371 — 374

To link to this Article: DOI: 10.1080/02770900902777791

URL: <http://dx.doi.org/10.1080/02770900902777791>

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ORIGINAL ARTICLE

The Ala Allele at Val762Ala Polymorphism in Poly(ADP-ribose) Polymerase-1 (PARP-1) Gene is Associated with a Decreased Risk of Asthma in a Turkish Population

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Background and objective. It has been suggested that inhibition of poly (ADP-ribose) polymerase-1 (PARP-1), either pharmacologically or by a gene knockout provides significant protection against systemic or tissue inflammation in animal models. The aim of this study was to analyze the association of the PARP-1 Val762Ala polymorphism, which has been reported to be associated with decreased enzymatic activity, in Turkish patients with adult asthma. **Methods.** A total of 112 subjects with stable asthma and 180 normal controls from the same geographic region were studied and polymerase chain reaction-based restriction analysis was used to identify Val762Ala polymorphism of the PARP-1. **Results.** In univariate analysis, PARP-1 762 AA genotype conferred a 3.4 fold reduction in risk (OR = 0.297, 95% CI = 0.105–0.813; P = 0.014), while heterozygous VA genotype conferred an even greater level of protection (OR = 0.06; 95%CI, 0.026–0.14; P < 10^{−6}). In addition, wild type PARP-1 762 V allele had 5 times the risk of developing asthma than those without the allele (OR 0.199, CI 0.118–0.334, P = 10^{−6}). **Conclusions.** These findings suggest that PARP-1 V762A variants may be one of the factors participating in protection or susceptibility to asthma in our population.

Keywords asthma, genetic susceptibility, SNP, poly(ADP-ribose) polymerase-1

INTRODUCTION

Asthma is a complex disease characterized by persistent airway inflammation giving rise to bronchial hyperresponsiveness and reversible airway obstruction. Although environmental factors are clearly important determinants of asthma, numerous studies have revealed that asthma has a strong genetic component but does not follow monogenic patterns of inheritance (1–3). The gene for poly (ADP-ribose) polymerase-1 (PARP-1, EC 2.4.2.30) may be one of the candidate genes for two reasons. It has been shown that inhibition of PARP activity by pharmacological inhibitors, or the absence of functional PARP enzyme in PARP knockout animals provides significant protection in animal models of a wide variety of diseases, including various forms of inflammation, shock, stroke, myocardial ischemia, diabetes, and diabetic endothelial dysfunction (4–6), and reduces the onset of the disease in murine models of asthma (7).

The protective effects of PARP inhibition and the PARP-1 knock out phenotype in asthma models have been attributed to inhibition of inflammatory signal transduction and of oxidative stress-induced cell dysfunction and tissue injury (8, 9). However, the precise mechanism underlying the role of PARP-1 enzyme in the inflammatory process is not clear.

PARP-1 is known to be involved in various cellular processes, such as DNA repair, genomic stability, transcription, stress response and cell death. Upon DNA damage, PARP-1 is activated and catalyzes the formation of poly(ADP-ribose)

chains by transferring (ADP-ribose) from β -NAD⁺ onto itself and nuclear acceptor proteins (see review 10). The PARP-1 activation has been also implicated in the initial inflammatory response by modulating expression of inflammation-related genes, like interleukin 1 (IL-1) (11, 12).

On the other hand, several nucleotide variants in the PARP-1 gene have been reported (13–15). There is growing evidence that single nucleotide polymorphisms (SNPs) of the PARP-1 gene are associated in a number of pathological conditions (16–20). Among these polymorphisms, the codon 762 variant (exon 17, 2444 T to C, V to A) is present in about 5 to 33% of the general population and causes about 40% decrease of PARP-1 activity. Wang et al. (21) have shown that the PARP-1 Val762Ala polymorphism reduces the enzymatic activity of PARP-1 by increasing Km.

If gene knockout or pharmacological inhibition of PARP-1 is correlated with the protective effects in asthma models, then it is possible that in +40329T $\rightarrow$ C(V762A) polymorphism of PARP-1 gene the Val allele may be associated as a risk factor with asthma. There are no publicly available data evaluating the association of PARP-1 Val762Ala polymorphism with asthma. Thus, we examined the Val762Ala polymorphism of PARP-1 in patients with asthma to determine its association with susceptibility of disease. In our present study, we looked for an association in a Turkish population of 180 healthy controls and 112 patients with asthma.

PATIENTS AND METHODS

One hundred and twelve patients with mild or moderate asthma who admitted to the outpatient asthma clinic of Cerrahpasa Medical Faculty Pulmonology Department have

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been recruited in the study. All patients had doctor diagnosed asthma and have been followed out at least for 6 months at the same department. Patients with asthma attack, severe disease, concomitant diseases such as heart insufficiency, coronary heart diseases, chronic renal diseases, diabetes were excluded from the study. Patients were requested to give 5 ml peripheral blood in order to participate in the study. Informed consent of the patients was obtained before drawing blood samples. All subjects gave written informed consent to participate in the study that was approved by the Medical Ethics Committee of the Istanbul University Cerrahpasa Medical Faculty in Istanbul.

Polymerase Chain Reaction (PCR)

DNA was isolated from the peripheral blood by the method of phenol-chloroform extraction (22). The codon 762 genotypes were determined using a PCR-RFLP assay (23). The primers used were as follows: 5'-TTTGCTCCTCCAGGCCAAC (mutated GC) G-3' and 5'-TGGAAGTTTGGGACCGCTGC-3', which generate a 210-bp fragment. The PCR reactions were performed in a 25- μ l reaction volume containing 200 ng of genomic DNA, 25 pmol of each primer, 0.2 mM each deoxynucleoside triphosphate, 1 $\times$ PCR buffer [10 mM Tris-HCl (pH 8.3) and 50 mM KCl], 1.5 mM MgCl₂, and 1 unit of Taq polymerase. The reaction was carried out in the following conditions: an initial melting step of 94 °C/5 min followed 35 cycles of 30 seconds at 94 °C, 20 seconds at 56 °C and 20 seconds at 72 °C and final elongation step 10 minutes at 72 °C. Five microliters of the PCR products were digested overnight with 5 units of BstUI at 60 °C. The digestion products were separated on 6% acrylamide gel and the codon 762 genotypes were defined with distinct band patterns: TT (Val/Val) (210) TC (Val/Ala) (210, 190, and 20 bp), and CC (Ala/Ala) (190 and 20 bp). As a quality control, the genotyping analysis was repeated twice for all subjects.

Statistical Analysis

Allelic frequencies were estimated by the allele counting method. Chi-squared (χ^2) analysis was used to compare the observed number of each genotype with those expected for a population in Hardy-Weinberg equilibrium and to compare genotype frequencies between asthmatics and control subjects. The association between genotypes and asthma risk was estimated by computing crude odds ratios (OR) and 95% confidence intervals (95% CI). All statistical analyses were performed with SPSS 11.5 software for Windows. Statistical significance was assumed at $p < 0.05$.

RESULTS

The basic demographic data of our patients and controls are shown in Table 1. All subgroups had similar age and sex distributions. The allele and genotype distributions of the PARP-1 Val762Ala polymorphism among cases and con-

TABLE 1.—Features of the studied subjects.

	Asthma patients	Controls	<i>p</i> -value
Mean age (years)	43.5 $\pm$ 17	45 $\pm$ 16.5	0.102
Female (%)	78.5	77	0.988
Race (Turkish) (%)	100	100	

TABLE 2.—PARP-1 Val762Ala polymorphism: Allele frequencies in patients with asthma and control subjects.

Allele	Cases (n = 112 ; 224 Alleles)	Controls (n = 180; 360 Alleles)	(<i>p</i> OR, 95% CI)
PARP-1 762 V (wt)	202 (90.1)	233 (64.7)	—
PARP-1 762 A	22 (9.8)	127 (35.2)	$< 10^{-6}$ (0.199, 0.118–0.334)

OR, odds ratio; CI, confidence interval; wt, wild-type.

Data are expressed as n (%).

Chi-squared test, $\chi^2 = 45.754$.

trols are shown in Tables 2 and 3. Although the genotype distribution of PARP-1 Val762Ala polymorphism was consistent with Hardy-Weinberg equilibrium in the control group ($p = 0.450$), the genotype distribution in the cases was significantly different from Hardy-Weinberg proportions ($p = 0.007$), with too few heterozygotes observed. The allele frequencies of the PARP-1 Val762Ala polymorphism were significantly different between cases and controls (PARP-1 V: 202 of 224 [90%] and PARP-1 A: 22 of 224 [10%] versus PARP-1 V: 233 of 360 [65%] and PARP-1 A: 127 of 360 [35%], respectively; $p < 10^{-6}$; OR 0.199, 95% CI 0.118–0.334).

PARP-1 762 VV genotype was more common in the case group (87%) than in the control group (39%). In the univariate logistic regression analyses, we observed that proportion of patients who were homozygote for PARP-1 762 AA was significantly lower than their respective controls, conferring a 3.36-fold decrease in asthma risk in 762 AA individuals when using the 762 VV wild-type homozygote genotype as a reference (OR = 0.297, 95% CI = 0.105–0.813; $p = 0.014$). This protective effect was even greater when the individuals with PARP-1 VA heterozygote genotype were compared with those with the VV homozygote genotype, resulting in a 16-fold reduction in asthma risk (OR = 0.062, 95% CI = 0.026–0.142; $P < 10^{-6}$).

DISCUSSION

Epidemiological and twin studies have demonstrated that asthma is under genetic and environmental influences. Several investigators have suggested that there may be several genetic risk factors that affect the susceptibility for this disease (1–3). PARP-1 may be a candidate gene, as PARP-1 deletion experiments and therapeutic approaches using PARP-1 inhibitors demonstrated improvement in systemic or tissue inflammation (4–7). It has been also shown that the PARP-1 activation has been implicated in the initial inflammatory response by modulating expression of inflammation related genes (9, 11, 12, 24). In addition,

TABLE 3.—Frequency distribution of PARP-1 gene Val762Ala polymorphism in patients with asthma and control subjects.

Genotype	Cases (n = 112)	Controls (n = 180)	<i>p</i> (OR, 95% CI) V/V versus AV or AA
PARP-1 762 VV	97 (86.6)	70 (38.8)	Reference
PARP-1 762 VA	8 (7.1)	93 (51.6)	$< 10^{-6}$ (0.062, 0.026–0.142)
PARP-1 762 AA	7 (6.2)	17 (9.4)	0.014 (0.297, 0.105–0.813)

OR, odds ratio; CI, confidence interval; wt, wild-type.

Data are expressed as n (%).

previous studies associated Val762Ala polymorphism with lower PARP-1 enzyme activation (21, 25). Therefore, it convinced us to examine the association between Val762Ala polymorphism and asthma in a Turkish population. Our expectation was that the Val allele might be present at higher frequencies in patients with asthma, although we did not find any significant correlation between this polymorphism and rheumatoid arthritis, which is another inflammatory disease (26).

As expected, the results presented here showed that PARP-1 762 Val allele is related to increased risk of asthma. In univariate regression analysis model, subjects with the PARP-1 762 V allele had 5 times the risk of developing asthma than those without the allele (OR 0.199, CI 0.118–0.334, $P=10^{-6}$). We also found that the genotypes of PARP-1 762 VA and AA were associated with a decreased risk of adult asthma, compared with their wild-type homozygotes. Therefore, we provide an evidence that an amino acid substitution variant in the PARP-1 gene may have a protective effect for asthma. As far as we know, there is no published study exploring the Val762Ala polymorphism of PARP-1 gene in patients with asthma. Hence, our results are not comparable to other literature data.

At present, the basis for the effect of the PARP-1 Val762Ala polymorphism on susceptibility to asthma remains unknown. As the production of TNF α and IL-12 was suppressed by PARP inhibitors (5, 27) and it has been demonstrated that PARP-1 is required for activation of several transcription factors in inflammation of several mediators (9, 19), the simplest hypothesis explaining the protective effect against the development of asthma of PARP-1 Val762Ala polymorphism, is that the decreased PARP-1 enzymatic activity associated with the Ala762 allele variant may affect expression of genes involved in inflammatory response, perhaps by altered inflammatory response.

Moreover, it can be similarly speculated how heterozygous PARP-1 762 VA genotype is more protective than the AA genotype, as it has been reported that the modulation of cytokine production by various stimulators was more strongly affected by heterozygous variant of some SNP in various genes than those from homozygote variant (28, 29). Therefore, heterozygosity for PARP-1 +40329T→C may confer a protective effect against asthma or the severity of asthma. However, these hypotheses require further investigations.

We acknowledge that there are some limitations to this study such as its relatively small size, and the fact that it only considered Turkish patients, whereas racial differences may be important. Secondly, we have not yet evaluated whether PARP-1 V762 variant may lead to deficient enzyme activity in asthma risk. On the other hand, as pretreatment with the PARP-1 inhibitors reduced the severity of cough and the occurrence of dyspea and delayed the onset of respiratory abnormalities (30), larger studies should test whether this genotype also plays a role in the severity of asthma.

In conclusion, the present findings suggest that Ala allele in codon 762 variant of the PARP-1 gene may be associated with a decreased risk of asthma disease. Extended analyses with a larger size should be carried out from different ethnic origins to further verify this association.

ACKNOWLEDGMENT

We would like to thank all of the subjects who participated in this study. This work was supported by Society of Medical Biologists.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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