

# Study of the relation between two common cyclooxygenase 2 gene polymorphisms with risk of developing and subtypes of vitiligo in Egyptian patients

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## Abstract

**Background/Purpose:** Genetic factors play an important role in the pathogenesis of vitiligo. Cyclooxygenase 2 (COX2) gene induced by ultraviolet radiation controls the synthesis of prostaglandins, which are found to be beneficial in treating vitiligo. COX2 gene polymorphism has been previously evaluated in Chinese population. We aimed to study the relation between two common COX2 gene polymorphisms with vitiligo and its subtypes among Egyptian patients.

**Patients and Methods:** This study included 200 participants (100 vitiligo patients and 100 healthy controls). COX2-765G/C and -1195A/G gene polymorphism was studied by restriction fragment length polymorphism polymerase chain reaction analysis and the results were compared between the two groups and among different subtypes of vitiligo.

**Results:** Frequency of COX2-1195 AA, AG, GG genotypes showed no significant association among patients with vitiligo ( $P = 0.626, 0.321, 0.08$ , respectively); those with generalized vitiligo ( $P = 0.739, 0.291, 0.101$ , respectively) and those with segmental vitiligo ( $P = 0.410, 1.00, 0.676$ , respectively) compared to the control group. Regarding COX2-765G/C genotypes, GG genotype was more frequent among patients with vitiligo [84 (84%)] compared to controls [63 (63%)] ( $P = 0.001$ ). GC genotype was significantly less frequent [15 (15%)] among patients compared to controls [32 (32%)] ( $P = 0.005$ ). Generalized and segmental types of vitiligo also showed no significant difference in the frequency of COX2-765G/C genotypes compared with controls.

**Limitations:** Being a pilot study, a relatively small number of participants were included.

**Conclusion:** COX2-1195A/G gene polymorphism is not associated with the risk of developing vitiligo or with vitiligo subtypes. COX2-765 GG genotype is associated with vitiligo, especially of the generalized type.

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## Introduction

Vitiligo is a common acquired depigmentation disorder of the skin manifested clinically as white macules.<sup>1</sup> Clinical presentation includes segmental, non-segmental, and mixed vitiligo.<sup>2</sup> Though its exact pathogenesis is not clearly known, vitiligo is considered as a multifactorial disease in which genetic and environmental factors play a role.<sup>4</sup>

According to genetic hypothesis, vitiligo has a multigenic inheritance. Several attempts have been made to identify a risk group pattern for vitiligo by genetic analyses.<sup>5</sup>

Prostaglandin E2 is synthesized in skin. It causes melanocyte proliferation; influences responsiveness of melanocytes to

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neuronal stimuli; induces changes in melanocytes necessary for transfer of melanosomes to surrounding keratinocytes, stimulates tyrosinase activity;<sup>6</sup> and enhances basic fibroblast growth factor mRNA expression<sup>7</sup> (the derived peptide of which is effective locally in vitiligo).<sup>8</sup> Oxidative stress, known to cause melanocyte destruction in vitiligo, results in a decrease in prostaglandin E2.<sup>9</sup> Prostaglandin E2 also inhibits apoptosis, stimulates inflammatory response, and promotes immunosuppression.<sup>10</sup> Topical prostaglandin E2 is a promising therapy for localized stable vitiligo.<sup>11,12</sup>

Cyclooxygenases are key enzymes that mediate the conversion of free arachidonic acid into prostaglandin H2 and other eicosanoids.<sup>13-15</sup> There are two major cyclooxygenase (COX) isoforms, COX1 and COX2. COX1 is constitutively expressed in most cell types, while COX2 is not normally expressed in most tissues, but can be induced to do so by several stimuli including growth factors, cytokines, and tumor promoters.<sup>16</sup> Ultraviolet radiation is a known stimulus for COX2 expression in the epidermis.<sup>17,18</sup> Ultraviolet-induced COX2 expression increases prostaglandin E2.<sup>19</sup>

COX2 gene is mapped to chromosome 1q25.2–q25.3 and is about 8.3 kb in size.<sup>20</sup> Polymorphisms may either eliminate or create binding sites for various factors, potentially altering the expression of COX2. Among the several single nucleotide polymorphisms in COX2, promoter polymorphisms COX2-1195A/G and -765G/C have been shown to modify COX2 transcription and messenger ribonucleic acid levels.<sup>21</sup> COX2-765G/C polymorphisms were associated with the production of prostaglandin E2.<sup>22</sup>

Considering the important role of COX2 in ultraviolet-induced prostaglandin E2 production; ethnic variations in the frequency of single nucleotide polymorphisms in the COX2 gene;<sup>23,24</sup> and the relation between some of these single nucleotide polymorphisms and the occurrence of vitiligo in Chinese population, we aimed to find out if two of the common COX2 gene polymorphisms were associated with a predisposition to vitiligo among Egyptian patients and if they were related to any specific disease subtypes.<sup>25</sup> Study of these polymorphisms among Egyptians has not been previously evaluated.

## Patients and Methods

### Patients

This study included 100 patients with vitiligo and 100 healthy individuals as controls. All participants were recruited from the dermatology outpatient clinics of Ain Shams University Hospital, Cairo, Egypt and National Research Centre, Giza, Egypt. Vitiligo was classified as segmental or nonsegmental.<sup>26</sup> Segmental vitiligo was diagnosed if the disease had a dermatomal distribution. Active vitiligo was defined as the appearance of new lesions or the enlargement of existing lesions in the three months before presentation.<sup>25</sup>

Age of the patients ranged from 10 to 71 years. Twenty-four patients were males and 76 were females. Twenty-four patients had positive family history of vitiligo. Age of the persons in the control group ranged from 11–73 years. Twenty-six patients were males and 74 were females. In the patients' group, disease duration ranged from 0.5 to 11 years. Ninety-two patients had generalized and 8 had segmental vitiligo. Sixty-nine patients had active and 31 had inactive disease.

All participants gave informed consent to participate in this work. The study was approved by the research ethics committee of National Research Centre, Giza, Egypt.

All participants were subjected to full history taking, general and dermatological examination, and venous blood sample collection for the study of COX2 -765G/C and -1195A/G gene polymorphisms.

## Methods

### Deoxyribonucleic acid extraction

Two ml venous blood samples were collected in the morning into ethylene diamine tetraacetic acid (EDTA) vacutainer tubes used for genomic deoxyribonucleic acid extraction. Extraction of genomic deoxyribonucleic acid from whole blood using purification of spin column QIA gene extraction kit was carried out.

### Genotyping of -765G/C and -1195A/G polymorphisms

Restriction fragment length polymorphism polymerase chain reaction analysis was used to amplify the COX2 polymorphisms (-765G/C and -1195A/G) according to Zhang *et al.*, 2005.<sup>21</sup> The primers used to amplify the target fragments containing these two polymorphisms were: 5'-TCTCACCTCA-CATGCTCCT-30 (forward) and 5'-TCTTTTCTGTCCACTTTTCCAA-3' (reverse) for COX2-1195A/G; 5'-ATGAGGAGAATTTACCTTTCGC-3' (forward) and 50-TTTTGTGGAATGAAATAGCTACCT-3' (reverse) for COX2-765G/C.

The polymerase chain reaction was performed in a total volume of 25  $\mu$ L using 10 pmol of each primer, 1.5 mM HgCl<sub>2</sub>, 200  $\mu$ M dNTPs, and 2U of Taq deoxy ribonucleic acid polymerase. The conditions were as follows: 35 cycles, each consisting of denaturation at 94°C for 30 seconds, annealing at 61°C for 30 seconds, and extension at 72°C for 30 seconds. The reaction cycles were preceded by 5 minutes denaturation at 94°C and were followed by 7 minute extension at 72°C.

The polymerase chain reaction products were confirmed by electrophoresis on 2% agarose gel and visualized by ethidium bromide staining.

### Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD). Categorical variables were expressed as frequencies and percentages. Student's *t*-test and analysis of variance (ANOVA) test were used to assess the statistical significance of the difference between two and more than two study group means, respectively. Chi square and Fisher's exact test were used to examine the relationship between categorical variables. Logistic regression was used for calculating odds ratio. A significance level of  $P < 0.05$  was used in all tests. All statistical procedures were carried out using statistical package for the social sciences (SPSS) version 15 for Windows (SPSS Inc, Chicago, Illinois, United States of America).

## Results

The mean age of patients was  $29.27 \pm 11.95$  years. Twenty four patients (24%) were males and 76 (76%) were females. Twenty-four (24%) of the patients had positive family history of vitiligo. Mean age of participants in the control group was  $28.18 \pm 10.56$  years. Twenty six (26%) among them were males and 74 (74%) were females. No statistically significant difference was found between patients' group and control group regarding age or sex ( $P = 0.360$  and  $0.744$ , respectively).

In the patients' group, the mean disease duration was  $2.7 \pm 1.78$  years. Ninety-two (92%) patients had generalized and 8 (8%) had segmental vitiligo. Sixty-nine (69%) had active and 31 (31%) had inactive disease.

#### COX2-1195A/G gene characteristics

Twenty seven (27%) among the vitiligo patients had COX2-1195 AA genotype compared to twenty four (24%) among controls ( $P = 0.626$ ). Fifty seven (57%) had AG genotype compared to fifty (50%) among controls ( $P = 0.321$ ). Sixteen (16%) had GG genotype compared to 26 (26%) among controls ( $P = 0.08$ ). [Table 1] Subgroup analysis of each of generalized vitiligo and segmental vitiligo against controls showed no significant difference regarding COX2-1195 AA, AG, and GG genotype frequencies ( $P = 0.739, 0.291, \text{ and } 0.101$  for generalized vitiligo vs. controls;  $0.410, 1.00, \text{ and } 0.676$  for segmental vitiligo vs. controls, respectively).

Comparison of vitiligo patients of different COX2-1195A/G genotypes with age and sex showed no significant difference ( $P = 0.566$  and  $0.688$ , respectively). Twelve (44.4%) patients with AA genotype had positive family history of vitiligo, compared to 4 (25%) with GG genotype and 8 (14%) with AG genotype ( $P = 0.010$ ).

Analyzing COX2-1195 AA, AG, and GG genotype carrier versus non-carrier patients with the different demographic data showed no statistically significant difference with age and sex ( $P = 0.4460$  and  $0.423$ , respectively, for AA genotype;  $0.955$  and  $0.427$ , respectively,

for AG genotype;  $0.397$  and  $1.00$ , respectively, for GG genotype). However, vitiligo carriers of COX2-1195 AA genotype had a significantly higher percentage of positive family history of the disease [12 (44.4%)] than non-carriers [12 (16.4%)] ( $P = 0.004$ ), while COX2-1195 AG genotype carriers showed a significantly lower percentage of positive family history of vitiligo [8 (14%)] than non-carriers [16 (37.2%)] ( $P = 0.007$ ); no significant difference was found among patients with COX2-1195 GG genotype in this regard ( $P = 1.00$ ). Furthermore, no statistically significant difference was detected regarding the disease duration, subtype and activity on comparing different COX2-1195 genotypes ( $P = 0.086, 0.874, \text{ and } 0.682$ , respectively) or between carriers and non-carriers of each genotype ( $P = 0.028, 0.443, \text{ and } 0.427$ , respectively, for AA genotype;  $0.189, 0.722, \text{ and } 0.770$ , respectively, for AG genotype;  $0.384, 1.00, \text{ and } 0.770$ , respectively, for GG genotype).

#### COX2-765G/C gene characteristics

Eighty four (84%) patients had GG genotype, fifteen (15%) had GC genotype, and one (1%) had CC genotype; whereas among controls, sixty three (63%) had GG genotype, thirty two (32%) had GC genotype, and five (5%) had CC genotype. GG genotype was significantly more frequent ( $P = 0.001$ ), while GC genotype was significantly less frequent ( $P = 0.005$ ) among patients than among controls. Frequency of CC genotype showed no significant difference between the groups ( $P = 0.200$ ). Persons with COX2-765 GC genotype had a 2.6-fold lower risk of having vitiligo [Table 1].

**Table 1: Comparison between vitiligo patients and controls regarding COX2-1195A/G and COX2-765G/C gene characteristics**

COX2 genotypes	Group		OR (95% CI)	P	Significance
	Control (N=100), N (%)	Cases (N=100), N (%)			
COX2-1195A/G genotypes					
AA					
Present	24 (24.0)	27 (27.0)	0.8 (0.45-1.6)	0.626*	NS
Null	76 (76.0)	73 (73.0)			
AG					
Present	50 (50.0)	57 (57.0)	0.75 (0.43-1.3)	0.321*	NS
Null	50 (50.0)	43 (43.0)			
GG					
Present	26 (26.0)	16 (16.0)	1.8 (0.9-3.7)	0.08*	NS
Null	74 (74.0)	84 (84.0)			
AA	24 (24.0)	27 (27.0)	1 (reference)		
AG	50 (50.0)	57 (57.0)	0.987 (0.5-1.9)	0.968 <sup>‡</sup>	NS
GG	26 (26.0)	16 (16.0)	1.8 (0.7-4.1)	0.155 <sup>‡</sup>	NS
COX2-765G/C genotypes					
GG					
Present	63 (63.0)	84 (84.0)	0.324 (0.16-0.63)	0.001*	HS
Null	37 (37.0)	16 (16.0)			
GC					
Present	32 (32.0)	15 (15.0)	2.6 (1.3-5.3)	0.005*	HS
Null	68 (68.0)	85 (85.0)			
CC					
Present	5 (5.0)	1 (1.0)	5.2 (0.5-45.4)	0.2**	NS
Null	95 (95.0)	99 (99.0)			
GG	63 (63.0)	84 (84.0)	1 (reference)		
GC	32 (32.0)	15 (15.0)	2.84 (1.4-5.6)	0.003 <sup>‡</sup>	HS
CC	5 (5.0)	1 (1.0)	6.6 (0.76-58.4)	0.087 <sup>‡</sup>	NS

\*Chi-square, \*\*Fisher exact test, <sup>‡</sup>Logistic regression. CI: Confidence interval, COX: Cyclooxygenase, HS: Highly significant, NS: Nonsignificant, OR: Odds ratio

Seventy seven (83.7%) patients with generalized vitiligo had GG genotype compared to 63 (63%) among controls ( $P = 0.001$ ). Fourteen (15.2%) patients with generalized vitiligo had GC genotype compared to 32 (32%) among controls ( $P = 0.006$ ). No significant difference was found between the two groups regarding CC genotype ( $P = 0.214$ ). *COX2-765* GC genotype had a 2.7-fold lower risk of having generalized vitiligo than controls [Table 2].

Comparison between segmental vitiligo group and controls regarding *COX2 -765G/C* gene characteristics showed no statistically significant difference ( $P = 0.256, 0.430, \text{ and } 1.00$  for GG, GC, and CC genotypes, respectively).

Comparison between vitiligo patients with different *COX2-765G/C* genotypes regarding age, sex, family history of vitiligo ( $P = 0.309, 0.078, \text{ and } 0.816$ , respectively), as well as disease duration, subtype, and activity showed no statistically significant difference between the two groups ( $P = 0.880, 1.00, \text{ and } 0.682$ , respectively).

Comparison between patients carrying *COX2-765* GG genotype and CC genotype versus non-carriers showed no statistically significant difference regarding age, sex, or family history of vitiligo ( $P = 0.780, 0.057, \text{ and } 1.00$ , respectively, for GG genotype;  $0.125, 1.00, \text{ and } 1.00$ , respectively, for CC genotype). Comparison between patients carrying and not carrying *COX2-765* GC genotype showed no statistically significant difference regarding age and family history of vitiligo ( $P = 0.890 \text{ and } 0.752$ , respectively), but females were more frequent among patients with *COX2-765* GC genotype ( $P = 0.047$ ).

Comparison between patients with and without *COX2-765* GG genotype, GC genotype, and CC genotype regarding disease duration, subtype, and activity showed no statistically significant difference ( $P = 0.822, 1.00, \text{ and } 0.770$ , respectively, for GG genotype;  $0.734, 1.00, \text{ and } 0.772$ , respectively, for GC genotype;  $0.697, 1.00, \text{ and } 1.00$ , respectively, for CC genotype).

## Discussion

Patients with vitiligo (including its generalized and segmental subtypes) did not show significant difference in the frequency of *COX2-1195A/G* genotypes when compared with a

control group. So, *COX2-1195A/G* gene polymorphism does not appear to affect the risk of developing vitiligo. Though the over all frequency of different genotypes of *COX2-1195A/G* was similar in our study population compared to a Chinese population as reported by Li *et al.*, they had reported that the risk of vitiligo was associated with the *COX2-1195A/G* polymorphism.<sup>25</sup> This difference may be because the effect of these gene polymorphisms may be different among different ethnic populations.

Frequencies of *COX2-1195A/G* genotypes did not seem to vary with age, sex, disease duration, subtype or activity. However, family history was found to be related with this polymorphism; as patients with *-1195* AA genotype showed a significantly higher percentage and patients with AG genotype showed a significantly lower percentage of positive family history of vitiligo. This denotes that *COX2-1195A/G* gene polymorphism may be related to familial occurrence of the disease.

Regarding *COX2-765G/C* polymorphism, we found that GG genotype was significantly more frequent whereas GC genotype was significantly less frequent among patients (including those with generalized vitiligo) compared to the control group. Patients with *COX2-765* GC genotype have a lower risk of having vitiligo and specifically the generalized type. So *COX2-765* GC genotype seems protective against vitiligo. This could be as a result of enhanced prostaglandin biosynthesis as a functional consequence of *-765G/C* polymorphism.<sup>21</sup> This finding is biologically rational as the *-765G/C* change also creates a binding element for the E2F transcription factor, a cyclin-dependent regulator of expression of several genes.<sup>21</sup> In contrast to generalized vitiligo, we found that the segmental type is not related to *COX2-765G/C* gene polymorphism. These results are contradictory to that of Li *et al.* which found no relationship between the *COX2-765* polymorphism and vitiligo risk.<sup>25</sup> It is possible that rare functional alleles are present in linkage disequilibrium with the alleles assessed in the present study.<sup>21</sup> Our results may explain the beneficial effect of topical prostaglandin E<sub>2</sub> in the treatment of localized vitiligo.<sup>11,12</sup>

Age, sex, family history of vitiligo, disease duration, subtype, and activity of disease did not vary significantly among patients with different *COX2-765G/C* genotypes. However, a significantly higher

**Table 2: Comparison between generalized vitiligo and controls regarding *COX2-765G/C* gene characteristics**

COX2 genotypes	Group		OR (95% CI)	P	Significance
	Control, N (%)	Generalized, N (%)			
GG					
Present	63 (63.0)	77 (83.7)	0.332 (0.16-0.65)	0.001*	HS
Null	37 (37.0)	15 (16.3)			
GC					
Present	32 (32.0)	14 (15.2)	2.6 (1.2-5.3)	0.006*	HS
Null	68 (68.0)	78 (84.8)			
CC					
Present	5 (5.0)	1 (1.1)	4.7 (0.54-41.7)	0.214**	NS
Null	95 (95.0)	91 (98.9)			
COX2-765G/C genotypes					
GG	63 (63.0)	77 (83.7)	1 (reference)		
GC	32 (32.0)	14 (15.2)	2.7 (1.37-5.7)	0.005‡	HS
CC	5 (5.0)	1 (1.1)	6.1 (0.69-53.6)	0.102‡	NS

\*Chi-square, \*\*Fisher exact, †Logistic regression. CI: Confidence interval, COX: Cyclooxygenase, HS: Highly significant, NS: Nonsignificant, OR: Odds ratio

frequency of females was noted among patients with *COX2* – 765 GC genotype. Considering that patients with *COX2*-765 GC genotype have a lower risk of having vitiligo, the possibility that females could be less susceptible to vitiligo than males needs further investigation.

Limitation of this work is the relatively small number of participants as this is a pilot study. Studies with a larger sample size are needed to validate our findings.

### Conclusion

*COX2*-1195A/G gene polymorphism was not related to the risk of developing vitiligo or to vitiligo subtypes in the Egyptian population studied. However, *COX2*-765 GG genotype was associated with a higher susceptibility to develop vitiligo especially of the generalized type. These results may support the possible beneficial effect of topical prostaglandins in vitiligo treatment.

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### Conflicts of interest

There are no conflicts of interest.

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