Association of Functional Polymorphism in Protein Tyrosine Phosphatase Nonreceptor 22 (PTPN22) Gene with Vitiligo

Biomarker Insights
Volume 15: 1–5
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DOI: 10.1177/1177271920903038

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ABSTRACT: The *protein tyrosine phosphatase nonreceptor 22 (PTPN22)* is associated with susceptibility to autoimmune diseases. The functional polymorphism in *PTPN22* at 1857 is a strong risk factor for vitiligo susceptibility in Europeans; however, controversy exits in other populations. Present study was aimed to determine whether the PTPN22 C1857T polymorphism confers susceptibility to vitiligo in Saudi Arabians. Genomic DNA was extracted and amplified using tetra primer amplification-refractory mutation system polymerase chain reaction (ARMS-PCR) method. The frequencies of allele T and genotype CT of PTPN22 C1858T polymorphism were significantly higher, whereas those of allele C and genotype CC were lower in patients as compared with controls ($P < 0.0001$). The genotype TT was absent in both the patients and controls. It is concluded that PTPN22 C1858T polymorphism is strongly associated with vitiligo susceptibility. However, additional studies are warranted using large number of samples from different ethnicities and geographical areas.

KEYWORDS: Biomarker, PTPN22, polymorphism, Saudi, Vitiligo

RECEIVED: December 23, 2019. **ACCEPTED:** January 8, 2020.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Vitiligo is an acquired, autoimmune skin disorder characterized by melanocyte loss resulting into progressive depigmentation of skin and hair.[1,2] The prevalence of vitiligo varies considerably with ethnicity and it affects 0.1% to 2% population worldwide.[1,3] Vitiligo causes cosmetic issues and high psychological burden.[4] According to a survey, more than 75% of patients with vitiligo consider their appearance as intolerable.[5] Vitiligo reduces the beauty, thus affecting the private and social life of the patients. It lowers self-esteem and imposes a social stigma and decreases quality of life.[6,7] Vitiligo has a high degree of psychiatric morbidity.[8]

Vitiligo is associated with an elevated risk of several autoimmune diseases (AIDs) including autoimmune thyroid disease, rheumatoid arthritis, psoriasis, adult-onset insulin-dependent diabetes mellitus, pernicious anemia, systemic lupus erythematosus, inflammatory bowel disease, alopecia areata, and Addison disease.[6,9-11] Various cases of malignant tumors have also been reported in association with vitiligo, including melanoma,[12,13] squamous cell carcinoma,[14] basal cell carcinoma,[15] breast cancer,[16] bladder cancer,[17] colorectal cancer,[18] leukemia,[19] and Hodgkin disease.[20] The coexistence of vitiligo and various cancers may be simply a coincidence or there may be shared etiological factors responsible for it. It has to be determined. Recently, Li et al[21] reported that the dysregulated immune system in patients with vitiligo influences cancer development and demonstrated the patterns of malignancies in patients with vitiligo of Taiwan. Vitiligo commonly shows familial aggregation and multifactorial mode of inheritance. It is a polygenic disease and several genes related to autoimmunity have been reported to be associated with the pathogenesis of vitiligo.[11,22-26]

The protein tyrosine phosphatase nonreceptor 22 (*PTPN22*) gene encodes a lymphoid protein tyrosine phosphatase (LYP) which is involved in autoimmunity by preventing spontaneous T-cell activation and T-cell development and inactivating T-cell receptor (TCR)-associated kinases and their substrates. PTPN22 is expressed in lymphocytes.[27]

PTPN22 gene is a non–human leukocyte antigen (HLA) risk factor, strongly associated with AIDs. Various polymorphisms in *PTPN22* gene have been linked with several AIDs. A single-nucleotide polymorphism (SNP) in exon 14 of the *PTPN22* gene (C1858T, rs2476601), has been associated with a number of dermatological and other diseases.[27-31] PTPN22 (C1858T) polymorphism is considered a risk factor for diseases due to significant production of autoantibodies.[32-37] In PTPN22 C1858T, the cytosine changes to thymidine at nucleotide 1858 resulting in an amino acid change from arginine to tryptophan at codon 620 (R620W), located in the polyproline binding motif P1. PTPN22 1858C/T polymorphism has been suggested to increase Lyp protein activity, which in turn inhibits T-cell signaling and results in a failure to delete autoreactive T cells during thymic selection. The

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association of this polymorphism is restricted to disorders that have a strong autoantibody component as it results in immune responses against autoantigens.[38]

Available literature on the PTPN22 (C1858T) polymorphism and vitiligo susceptibility is inconsistent[26,38-40] and further studies from different ethnic populations are required to confirm it. In the present study, the association of PTPN22 C1858T (R620W) polymorphism with the susceptibility to vitiligo was investigated in a Saudi cohort.

Materials and Methods

Patients and controls

A total of 325 subjects were recruited from Dermatology Clinic of Prince Sultan Military Medical City (PSMMC), Riyadh Saudi Arabia. Biologically unrelated Saudi patients with vitiligo (64 males and 61 females) aged 6 to 79 years (mean 27.85 ± 12.43 years) and matched healthy subjects (143 males and 57 females) aged 20 to 65 years were included in this study. The subject/parent agreed for participating in the study was asked to sign the consent form before recruitment. All the subjects consented to participate in the study. The diagnosis of vitiligo was performed by a dermatologist. Subjects with history of any other autoimmune disorder were excluded. Controls having first- or second-degree relative with vitiligo or any autoimmune disorders were also excluded to minimize genetic heterogeneity. Power was calculated online (http://www.stat.ubc.ca/~rollin/stats/ssize/caco.html). Study protocol was approved by the research and ethical committee of the MSD.

DNA amplification by polymerase chain reaction

Genomic DNA was extracted from the venous blood of patients with vitiligo and controls using a QIAamp DNA mini kit (Qiagen, CA, USA). Genomic DNA was amplified for detection of PTPN22 R620W (rs2476601) polymorphism following the method as outlined by Kouhpayeh et al.[41] Amplification of the human growth hormone gene was included as positive control in the polymerase chain reaction (PCR) assay. Details of primer sequences, PCR cycling conditions, and product size were mentioned in our earlier publication.[31] The PCR products were electrophoresed on 2% agarose gels and photographed. To verify the initial results and ensure genotyping quality, 25% of the samples (randomly selected) were re-genotyped.

Statistical analysis

The Fisher exact test was used to analyze genotypes and alleles frequencies. The errors due to multiple comparison tests were minimized by Bonferroni correction. *P* values indicating statistical significance are depicted in Table 1. Relative risk (RR) indicated by odds ratios, etiologic fraction (EF), and preventive fraction (PF) was calculated as described elsewhere.[42,43]

Table 1. Demographic characteristics of patients and controls.

Age of patients (range [mean ± SD]), y	6-79 [27.85 ± 12.43]
Gender (male:female)	64:61
Age of onset (range [mean ± SD]), y	2-60 [22.57 ± 15.42]
Duration of disease (range [mean]), y	1-19 [6.2]
Type of vitiligo	
Generalized	34%
Focal	34%
Acrofacial	19%
Lip-tip	12%
Universalis	1%
Controls	
Gender (male:female)	143:57
Age range, y	20-60

Results

Demographic data and clinical characteristics of patients with vitiligo are presented in Table 1. All patients had nonsegmental (generalized or localized) type of vitiligo. The number of controls per case was 1.6 and yielded a power of 96%. The frequencies of variants of PTPN22 (C1858T) in patients with vitiligo and controls are summarized in Tables 2 and 3. The distributions of the genotype and allele frequency PTPN22 (C1858T) were in Hardy-Weinberg equilibrium in control group (χ^2 test $P = 0.5816$), but the frequencies differed significantly in patients compared with controls (Table 1). The patient group had significantly higher frequency of allele T than the control group. On the other hand, controls had increased frequency of allele C as compared with patients ($P < 0.0001$, $P < 0.004$ Bonferroni corrected). The frequency of heterozygous genotype CT was significantly higher in patients than in the controls ($P < 0.0001$, $P < 0.004$ Bonferroni corrected). The frequency of CT in controls (7.5%) corresponded to the frequency of minor allele (0.037), whereas it is very high (89.60%) in patients with vitiligo. In contrast, homozygous genotype CC was significantly decreased in patient group (10.4%) in comparison with controls (92.5%) ($P < 0.001$, $P < 0.004$ Bonferroni corrected). The homozygous TT genotype of PTPN22 (C1858T) polymorphism was totally absent in both the patient and control subjects.

Upon stratification of results in to males and females, there was no significant difference in the frequencies of genotypes and alleles in 2 sexes (Table 3) which indicated that sex has no effect on the prevalence of different variants of PTPN22 (C1858T) in the test population. Re-genotyping of 25% of the randomly selected samples yielded same result with 100% success. Thus, the variations due to procedural error were ruled out.

Table 2. Genotype and allele frequencies of PTPN22 variants in patients with vitiligo and matched controls.

GENOTYPE/ALLELE	VITILIGO (N=125)		CONTROL (N=200)		*P* VALUE	RR	EF[c]/PF	ODDS RATIO (95% CI)
	N	%	N	%				
CC	13	10.40	185	92.50	<0.0001[a,b]	0.009	0.88	0.009 (0.0043-0.020)
CT	112	89.60	15	7.50	<0.0001[a,b]	97.78	0.87[c]	106.26 (48.76-231.53)
TT	0	0	0	0	–	–	–	–
C-allele	138	55.20	385	96.25	<0.0001[a,b]	0.047	0.84	0.048 (0.0271-0.0851)
T-allele	112	44.80	15	3.75	<0.0001[a,b]	21.17	0.83[c]	5.681 (3.897-8.280)

Abbreviations: n, number of allele/genotype; RR, relative risk; EF, etiological fraction; PF, preventive fraction; CI, confidence interval.
[a]Statistically significant using Fisher exact test.
[b]$P < .004$ Bonferroni corrected.
[c]Data for EF.

Table 3. Genotype and allele frequencies of PTPN22 variants in male and patients with vitiligo.

GENOTYPE/ALLELE	MALE (N=64)		FEMALE (N=61)		*P* VALUE	ODDS RATIO (95% CI)
	N	%	N	%		
CC	7	10.94	6	9.84	1.00	1.125 (0.355-3.561)
CT	57	89.06	55	90.16	0.78	0.888 (0.280-2.810)
TT	0	0	0	0	–	–
C-allele	71	55.47	67	54.92	1.00	1.022 (0.621-1.683)
T-allele	57	44.53	55	45.08	1.00	0.978 (0.594-1.610)

Abbreviation: CI, confidence interval; n, number of subjects.

Discussion

Significantly higher allele T and genotype CT frequencies in patients with vitiligo than controls indicated that PTPN22 (C1858T) polymorphism is significantly associated with the vitiligo susceptibility in Saudis. Various published reports on PTPN22 (C1858T) polymorphism support the association of the T-allele and vitiligo susceptibility in different ethnic populations. It has been reported to be a risk factor for vitiligo in English, Romanian, North American, Mexican, and South Indian Tamil populations.[11,26,44,45] A genome-wide association study indicates that PTPN22 (C1858T) is associated with vitiligo in European-derived white patients.[46] A meta-analysis using data from different ethnicities shows an association of PTPN22 (C1858T) with vitiligo in European but not in Asian population.[40]

In contrast, no significant association of PTPN22 C1858T polymorphism with susceptibility to generalized vitiligo was found in Indian Gujarat population, Jordanian, Egyptian female, and Turkish population.[39,47-49] Available literature shows that a variant of PTPN22 C1858T is responsible for increased risk of vitiligo in white patients; however, among nonwhite/Asians, inconsistency exits and even the 2 populations of same country differ in association with PTPN22 C1858T with vitiligo indicating the role of ethnicity. The heterozygous CT genotype, of the PTPN22 C1858T, has a strong association with nonsegmental vitiligo in South Indian Tamils, whereas there is no association of this polymorphism in Indian Gujarat population.[26,47] Our results suggest a very strong association of PTPN22 C1858T with vitiligo in Saudi Arabian population. These difference in results of this polymorphism in Asian or nonwhite can be attributed to ethnic differences. PTPN22 1858T-allele has been reported to have a strong association with the risk of a number of autoimmune diseases such as Graves' disease, type 1 diabetes, psoriasis, rheumatoid arthritis, juvenile inflammatory arthritis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, Addison disease, Hashimoto thyroiditis, myasthenia gravis, and celiac disease.[31, 32,36,50-52]

In C1858T polymorphism at codon 620 of *PTPN22* gene, C changes to T. As T-allele encodes tryptophan (W) while C-allele encodes arginine (R) therefore this polymorphism results in an amino acid change from arginine to tryptophan. The functional significance of PTPN22 (C1858T) has been discussed by various workers.[44,53-55] It has also been shown experimentally that Trp620 prevents the interaction of LYP with C-terminal Src kinase.[55] As a result, T cells are activated in uncontrolled manner by the kinases associated with TCRs, ultimately increasing the immune system reactivity and predisposing an individual to AIDs.[44,53,55] Rajendiran

et al[26] found higher levels of PTPN22 in plasma of patients with vitiligo than controls and suggested that possibly activated T-helper cells may be responsible for the autoimmune mechanism in vitiligo as weak and reduced signaling of TCR plays a significant role in autoimmunity.

The assertion that the autoimmune-associated LYP with tryptophan at position 620 results into reduced TCR-mediated signaling is supported by another report by Vang et al.[56] Eventually, the T-cell differentiation is affected by this imbalanced signaling which favors Th1 responses.[56]

On the other hand, some studies advocates that the T-allele of PTPN22 (C1858T) is a hypomorphic variant and has a diminished function and cannot inhibit the TCR signaling in T cells correctly and consider LYP-620Trp as a loss-of-function.[45,53,54] This impaired LYP function in T cells may drive hyper responsive B cells to break the tolerance in the periphery and to produce autoantibodies, which lead to disease development.[54]

In our study, genotype TT is absent in both patients with vitiligo and healthy controls. Similarly, the absence of genotype TT has also been reported in earlier studies.[47,48] The frequency of CT genotype in patients (89.6%) is very high as compared with the control population (7.5%), indicating that carriers of CT genotypes are at a higher risk of developing vitiligo and this variant disturbs the immunity and contributes to vulnerability to the autoimmune mechanism in vitiligo.

This report substantiates the evidence convincing the role of *PTPN22* as an important genetic risk factor for autoimmune diseases. The results of present study will not only help in identifying the persons at higher risk of having other autoimmune disorders but also help in designing appropriate therapeutic and prophylactic measures. However, further studies using larger number of subjects from various ethnicities are needed for a better understanding of the association between autoimmunity and vitiligo as suggested by Akbas et al.[39] Although the possible reason for the lack of any relationship in some ethnicities may be the differences in genetic profile of different populations, but the false-negative results due to methodology errors cannot be excluded. The observed association of PTPN22 C1858T with vitiligo in Saudis was more prominent than reported for other populations. The strong association in Saudi patients may be correlated with high rate of consanguinity together with being a closed society. However, the relationship between *PTPN22* C1858T and manifestation of vitiligo warrants more studies, with larger population size as the immune dysregulation in vitiligo may be due to the interplay between environmental and genetic factors similar to other autoimmune diseases.

Acknowledgements

The authors thank MSD for providing all facilities.

Author Contributions

MA conceived and designed the experiment; GBH, FAH, ASA, and AA performed clinical examinations and collected demographic data; MA extracted DNA and performed genotyping; MA and AA-A analyzed the data, interpreted the results, and drafted the manuscript; GBH, FAH, ASA, AA, and AA-A agreed with manuscript results and conclusions; AA-A and MA revised, supervised, and approved the final version. All authors read and approved the final manuscript.

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