Original Article

Comparative case control study of clinical features and human leukocyte antigen susceptibility between familial and nonfamilial vitiligo

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ABSTRACT

Background: Various studies worldwide suggest that human leukocyte antigen (HLA) region may be involved in the genetic susceptibility of vitiligo but little information is available from India. **Aim:** To find the HLA associated susceptibility to develop vitiligo in Indian patients and to detect role of HLA in familial vitiligo. **Methods:** This was a case controlled study which included all patients suffering from vitiligo over a period of one and half years. Clinical details were noted and sera collected from these patients were screened for the presence of HLA class I antibodies. The clinical features and HLA antigens were assessed and comparison was made between patients with familial and nonfamilial vitiligo. **Results:** Out of 114 patients studied, 84 had family history and 30 had no family history. Patients with family history of vitiligo have higher chances of acquiring vitiligo if first degree relatives are affected compared to if second degree relatives are affected. Family history of vitiligo is associated with an early onset of vitiligo (<20 years). There was no statistically significant difference in the type, stability, and severity of vitiligo in both the groups. HLA results in both the groups revealed increase in HLA A2, A11, A31, A33, B17, B35, B40, and B44 alleles while HLA A9, B13, and B53 alleles were decreased. Family history was associated with HLA A2, A28, A31, and B44 alleles. Early onset of vitiligo (<20 years) was significantly associated with HLA A2, A11, B17, B35, and B44 alleles. The patients with severe affection (>10% area) showed in significant association with HLA A10 and B8. **Conclusion:** Family history of vitiligo is associated with an early onset of vitiligo. There is no correlation of family history with the type of vitiligo, stability of lesions, and areas involved. Severity is not associated with family history. Apart from other alleles, alleles A2, and B44 play a significant role in vitiligo in the Indian patients.

Key words: Familial vitiligo, HLA alleles

INTRODUCTION

Vitiligo is an acquired pigmentary disorder of the skin with many social implications in India. The prevalence in India is in the range of 0.46–8.8%.[1] Autoimmunity, neurogenic cause, melanocyte self destruction, biochemical metabolic abnormality have all been proposed as causes. In addition, genetic influences play a significant part, as familial aggregation of cases has been noted.[2] In the past two decades, the autoimmune hypothesis had received the most attention because of the frequent coexistence of vitiligo with other autoimmune disorders. Besides humoral immunity cell mediated immunity has also been implicated in vitiligo ten years ago.[3] Human leukocyte antigen (HLA) association in vitiligo patients from other countries has been defined. However, no similar studies have been done here in various ethnic groups. Finding HLA association may be helpful in answering queries by parents with vitiligo about likelihood of their child developing vitiligo. In an effort to find answers to these questions we have compared clinical features and HLA phenotypes of patients with familial and nonfamilial vitiligo.

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METHODS

This was a case controlled study carried out in skin OPD of a tertiary care center after obtaining permission from Ethics Committee for Research on Human Subjects. All patients attending the vitiligo clinic were included over a period of one and half years, from October 2005 to May 2007. Clinical details including age, sex of patient, age of onset, sites involved, type of vitiligo, stability of lesions (no new lesions and no increase in the size of previous lesions since six months to one year) and severity of vitiligo were recorded. Parents were asked about similar type of lesion in other family members. Diagnosis in all cases was made on typical history of depigmented lesions with or without progression, clinical examination done and confirmed with Wood's lamp examination. A total of 5 ml blood was drawn from patients. Sera collected from these patients were screened for the presence of HLA class I antibodies. Known HLA typed reference lymphocyte panel available in the laboratory was used to characterize HLA A and HLA B locus antigen specificities. A total of 656 age and sex matched healthy controls from the same ethnic background were used as controls. National Institute of Health's two stage microlymphocytoxicity test was used for HLA typing.

RESULTS

Demographic profile: A total of 114 patients with vitiligo were studied. Out of these patients, 84 (73.7%) had family history and 30 (27.4%) had no family history. First degree relatives were affected in 45 (53.57%) patients and second degree relatives were affected in 24 (28.57%) patients. Patients with family history of vitiligo had higher chances of acquiring vitiligo if first degree relatives were affected than if second degree relatives were affected, which was statistically significant (Z value >1.96, using standard error of difference between two means). Out of 114 patients, those with age of onset before 20 years were 65 (57%): {familial patients: 53 (63%) and nonfamilial patients: 12 (40%)}. The average age of onset was younger (20 ± 15.07 years) in familial patients compared to nonfamilial patients (26.33 ± 16.67 years), the difference being statistically significant (*P* value = 0.0474, using unpaired *t* test).

Clinical profile: 19 out of 84 patients (16.66%) in the familial group had severe disease (>10% body area involved) and four patients out of 30 (13.33%) in the nonfamilial group had severe disease. The predominant sites of involvement were the extremities in both the groups, though involvement of trunk was statistically significant in familial vitiligo patients ($P = 0.01$, using Fischer's exact test). Fifty seven (67.9%) of familial patients had unstable vitiligo, whereas 19 (63.3%) of nonfamilial patients had unstable vitiligo. Vitiligo vulgaris was the most common type of vitiligo seen in both the groups, in 52 (61.90%) of the familial patients and 16 (53.33%) of the nonfamilial patients. There was no statistically significant difference in the type of vitiligo, stability and severity of vitiligo in both the groups.

HLA profile: HLA results in both the groups revealed statistically significant ($P < 0.05$, Chi-square test) increase in HLA A2, A11, A31, A33, B17, B35, B40, and B44 alleles while HLA A9, B13, and B53 alleles were decreased. Family history was significantly ($P < 0.05$, Chi-square test) associated with HLA A2, A28, A31, and B44 alleles. Early onset of vitiligo (<20 years) was significantly associated with HLA A2, A11, B17, B35, and B44 alleles ($P < 0.05$, Chi-square test). Patients with severe affection (>10% area) showed association with HLA A10 and B8 which was not statistically significant ($P < 0.072$, Chi-square test).

DISCUSSION

The genetic association between HLA and predisposition of vitiligo is intriguing. Out of 114 patients included in our study, 84 (73.7%) had a positive family history and the remaining 30 had no family history. The higher number of familial cases in our study was due to the fact that we were placing a special emphasis on patients with positive family history. Available literature depicts the occurrence of family history in the range of 4% to 40%.[4–6] The average age of onset was significantly younger in familial patients ($P = 0.0474$) than in nonfamilial patients, which is marginally statistically significant. Our finding is consistent with the fact that family history of vitiligo may have an effect on the age of onset of vitiligo as noted in other studies.[2,7,8]

In our study, we noted that there was no statistically significant difference between familial and nonfamilial cases with regards to the severity of the disease i.e., more than 10% body area involvement. Our study emphasizes on the fact that family history

of vitiligo is not predictive factor for the severity of the disease. This is a useful data to dispel the myth that family history of vitiligo is associated with more severe disease in their offspring. In our study, the predominant sites of involvement were the extremities in both the groups. However, the involvement of the trunk along with other sites was significantly observed in familial patients compared to nonfamilial cases (P value <0.05). Although statistically significant, biological significance can not be elucidated and no specific reasons could be thought of or speculated for this finding. Regarding the stability of the disease, there was no significant association with family history. Vitiligo vulgaris was the most common type of vitiligo seen in both groups. There was no significant difference in the type of vitiligo in both the groups. Thus, clinical features such as distribution, extent of lesions, type of vitiligo, severity of disease did not show any statistically significant differences between familial and nonfamilial patients. These results match the results of a study done by Ando *et al*.[2]

HLA Analysis: Several studies have reported increased or decreased frequencies of specific class I and II MHC alleles in vitiligo patients although only a few remain statistically significant and have been confirmed in multiple populations. In our study, there was increased incidence of HLA A2, A11, A31, A33, B17, B35, B40, and B44 alleles while HLA A9, B13, and B53 alleles were decreased. Associations from other populations are given in Table 1.

Alleles A2, A31, and B40 have been previously reported in other populations as well. However, additionally the alleles A11, A33, B17, B35, and B44 have been found to be associated in Indian patients. This finding in Indian patients is new and similar associations are not reported from other populations. HLA A2 was significantly associated with vitiligo patients in our study also. HLA A2 has been associated with recognition of influenza A virus. Whether this is a precursor for vitiligo to develop is not yet clear and requires further investigation.[7] Interestingly, relationship has also been observed between regressing melanoma and HLA A2. In such cases of regressing melanoma and vitiligo, melanocyte specific cytotoxic T lymphocytes seem to be the cause of depigmentation.[23]

Family history was significantly associated with HLA A2, A28, A31, and B44 alleles. A very few studies exist in the literature [Table 2] about HLA associations in familial cases of vitiligo, none of which mentions the association of HLA A2, A28, A31, and B44 alleles. Hitherto, some new associations are described.

This apparent difference in HLA phenotype suggests a different genetic background of familial and nonfamilial vitiligo, which needs to be studied further.

Early onset of vitiligo[26,27] (20 or < 20 years) was significantly associated with HLA A2, A11, B17, B35, and B44 alleles. Associations from other populations are mentioned in Table 3. Thus, this supports the hypothesis of an immunogenetic influence on the expression of vitiligo.

Table 1: Human leukocyte antigen associations of vitiligo in different populations

Origin	Associated specificity in Vitiligo
China[2,7,9,10,11]	A2,A10, A30, A31, B13, B15
Italy (Northern)[12,13]	A30, Cw6, DQw3, DR6
Kuwait[14]	B21, Cw6
Oman[15]	Bw6, DR7
American (Blacks)[16]	A1, A2, A31, DR4
Dutch[17]	DR6
Turkey[18]	DR3, DR4, DR7
Morocco (Jewish)[19]	B13
Yemen[19]	Bw35
Germany (Northern)[20]	A2
Slovakia[21]	A2, Dw7
Holland[22]	DR4, C4BQ0
Other Asian studies[2,7,10,11]	A3, B18, B46, A31, Cw4
Our Study	A2, A11, A31, A33, B17, B35, B40, B44

Table 2: Human leukocyte antigen associations of familial vitiligo in different populations

Origin	Alleles associated with family history
Japan[2]	Bw46
Oman[15]	Bw4
European-American Caucasian families[8]	DRB1*04
Other studies[20,24,25]	DR4, DQw3
Our study	A2, A28, A31, B44

Table 3: Human leukocyte antigen associations of early onset of vitiligo in different populations

Origin	Alleles associated with early onset
Jews (Morocco)[19]	B13
Yemen[19]	Bw35
American blacks[24]	DR4
Our study	A2, A11, B17, B35, B44

In our study, alleles A10 and B8 have not been associated with severe vitiligo.

Some HLA alleles are proven to be protective against the occurrence of vitiligo. Protective antigens in populations are as follows—DQ2 is protective in North Italians;[13] A19 in Kuwaiti patients;[14] A10 in American blacks;[16] Cw7 in Dutch people;[17] A28 and B46 in Chinese patients;[22] and A9 and B5 in Saudi patients.[28] In our Indian patients, the protective alleles were A9, B13, and B53.

Thus, we can conclude that family history of vitiligo is associated with an early onset of vitiligo. There is no correlation of family history with the type of vitiligo, stability, and areas involved. Severity is not associated with family history. Apart from other alleles, alleles A2 and B44 play a significant role in vitiligo in Indian patients as they are involved in the familial aspect as well as play a role in the early onset of the disease.

However, HLA Class II alleles could not be done due to lack of funds. We recommend further studies with larger populations and inclusion of HLA class II alleles.

Overall, our results indicate that variation within the major histocompatibility complex contributes to the unique characteristics of vitiligo including earlier onset of vitiligo and association of specific alleles with family history.

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