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Do Clinical Variants of Vitiligo Involve X-Chromosomal Gene(s) Too?

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Vitiligo is a common complex skin disorder characterized by macular depigmentation of skin, varying in size and shape caused by destruction of melanocytes. A number of environmental and genetic factors have been implicated in the etiology of vitiligo. The heterogeneity observed at clinical level needs to be evaluated for an underlying genetic heterogeneity involving autosomal and X-linked loci. Based on the clinical symptoms, vitiligo is broadly classified into non-dermatomal and dermatomal. In order to understand the various etiological/pathophysiological factors responsible for different classes of vitiligo 3551 patient's clinical data of Indian origin was analyzed. The cases were grouped into different classes based on the lesion type at the time of disease presentation. A significant gender variation with male preponderance was observed in mucosal and acrofacial compared to other classes. 2:1 male to female ratio in clinical variants of vitiligo has been observed and has been used as a basis to hypothesize the involvement of X-linked gene(s) along with autosomal genes in the susceptibility to this polygenic condition.

Key words: Vitiligo, clinical variants, gender variation, autosomal and X-linked genes

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INTRODUCTION

Vitiligo is the depigmentation disorder which affects 0.1-2% of various populations world wide causing disfigurement and serious disturbances in the well being of the individual (Bolognia *et al*., 1998; Hann and Nordlund, 2000). Its incidence ranges from 0.1 to >8.8% across India (Srivastava, 1994; Shwartz and Janniger, 1997; Hann *et al*., 1997; Kovacs, 1998; Agarwal, 1998; Handa and Kaur, 1999; Alkhateeb *et al*., 2003). Family history of the disease differs from one part of the world to other and ranges from 6.25-18% in India (Virendra and Srivastava, 2007).

Vitiligo is a benign disorder which shows no influence on the physical capabilities or the life span of an individual but has tremendous effect on the psychological and social life (Behl *et al*., 1999). It is characterized by macular depigmentation of varying sizes or shapes, localized or generalized, single or multiple with a tendency to progress gradually with lesions enlarging and extending until a quiescent state is reached. Based on clinical symptoms, vitiligo is classified into dermatomal (segmental) and non-dermatomal (non segmental) which are further sub-classified into different classes. However, there is no standard approach to the classification. Vitiligo may be restricted or spread all over the body taking several months to years. The affected areas show destruction or weakening of melanocytes. There is no sex or age exempted with respect to Vitiligo (Arican and Kurutas, 2008; Schwartz *et al*., 2005).

A number of genetic and environmental factors have been implicated in the etiology of vitiligo. The heterogeneity of the disorder is explained on the basis of involvement of various factors like autoimmunity, neural and oxidative stress (Ochi and DeGroot, 1969; Macaron, 1977; Namazi, 2005; Donmez-Altuntas *et al*., 2008). A range of triggering factors is associated with the induction of vitiligo such as physical (harmful radiations), chemical (phenolic compounds), mechanical (injuries) and biological (viral infections) in nature.

The treatment of vitiligo is prolonged and includes medicines like topical corticosteroids, systemic PUVA (Psoralen+Ultraviolet A), topical PUVA, narrowband and broadband UVB (Ultraviolet B), micro phototherapy-UVB, Monochromatic Excimer Light (MEL) accounting for 40-80% repigmentation (Jane and Neil Prose, 2005) and surgical treatments including epidermal grafting, epidermal cell transplantation and cosmetic cover-ups. However, high interindividual variation exists in the outcome of the various therapeutic modes.

Understanding the etiology/pathophysiology of vitiligo could help in the management and the cure for this disorder. Despite much research, the mechanism of initiation of melanocyte destruction and progression of disease is not yet clear (Arican and Kurutas, 2008). Lack of reproducible results from different populations and ethnic groups may partly be attributed to the differences in clinical classification and pooling up of the data of genetically heterogeneous groups of vitiligo by various investigators. However, genome wide screenings have suggested a number of candidate genes in the occurrence of vitiligo that are scattered all over the genome (Pamela *et al*., 2003; Richard *et al*., 2004; Jian *et al*., 2005). Resolving genetic heterogeneity is crucial for gene mapping and studies should be carried out in homogenous groups than in heterogeneous groups.

The objective of the present study is to identify factors in the clinical heterogeneity that may help to categorize vitiligo individuals into different homogenous groups for further gene analysis studies.

MATERIALS AND METHODS

In the present study, 3551 patient's data has been collected from the hospital records of Central Research Institute for Unani Medicine (CRIUM) Hyderabad, India. The information collected includes demographical, clinical, family history and socio-economic status of the patients from 2004-2006.

Since, there is no standard protocol given to classify vitiligo, the classification used by different study groups varies (Moretti, 2003; Virendra and Srivastava, 2007) which in turn confuses while comparing the data of various studies. It is assumed that the underlying heterogeneity in the etiology of different classes of vitiligo reflects at the clinical level. Hence, pooling all the different categories of vitiligo for analysis will not bring out the specific underlying causes. Keeping this in view, in the present analysis patients were categorized into five different classes of vitiligo based on the clinical features at the time of disease presentation *viz*., non-dermatomal: generalized that shows multiple and large bilaterally distributed patches any where on the body; dermatomal: one or two lesions that show unilateral distribution along the dermatome; mucosal: that involves exclusively mucosal regions such as lips and genitals, acrofacial: affecting face and distal extremities and focal: that shows small one or two lesions restricted (Fig. 1). In each category, age of onset, sex ratio, extension of the lesion, disease status and family history have been taken into consideration.

Statistical analysis was carried out using statistical package for social sciences (SPSS version 15.00 software

Fig. 1: Photos depicting different classes of vitiligo (a) Non dermatomal, (b) Dermatomal, (c) Mucosal, (d) Acrofacial and (e) Focal

package) in the present analysis. Descriptive statistics such as percentages, mean and standard deviation were used for various parameters (classes of vitiligo, sex ratio, family history and age at onset). Chi-square test ($p<0.05$) and mixed model analysis ($p<0.05$) was applied to see the significance of gender variation in different classes of vitiligo.

RESULTS

The present study included 3551 vitiligo patients of Indian origin and the analysis of data has shown high frequency of non-dermatomal patients (57.67%) compared to dermatomal (19.66%), followed by mucosal (11.45%), acrofacial (5.65%) and focal (1.54%) (Fig. 2).

The data includes age ranges from <1 to 85 years. When age of onset was considered in the analysis, overall, the maximum number of individuals have fallen in

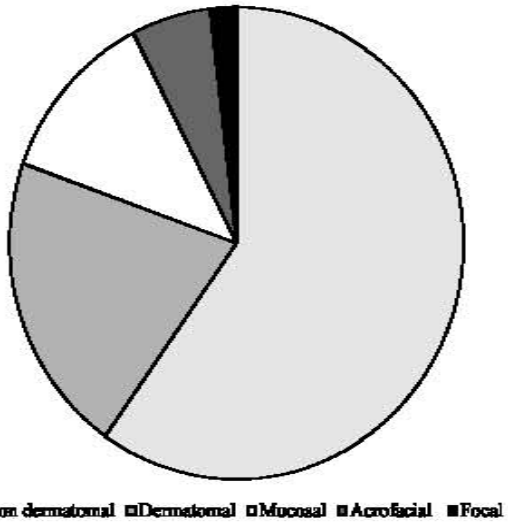

Fig. 2: Relative frequency of different classes of vitiligo

Table 1: Mean age at onset in different classes of vitiligo

Class of vitiligo	No. of vitiligo patients (male/female)	Age of onset (Mean±SD)
Non dermatomal (I)	2127 (1123/1004)	22.51±15.50
Dermatomal (II)	738 (386/352)	20.89±15.28
Mucosal (III)	430 (288/142)	25.96±14.52
Acrofacial (IV)	200 (128/72)	26.87±16.37
Focal (V)	58 (29/29)	20.86±15.45
Total	3551 (1954/1597)	22.86±15.48

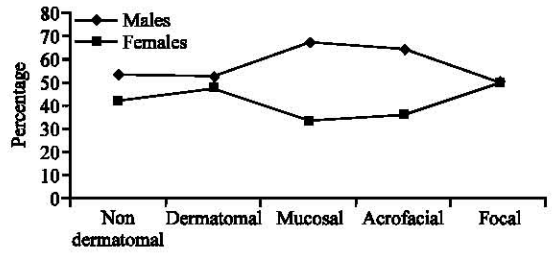

Fig. 3: Sex ratio in different classes of vitiligo

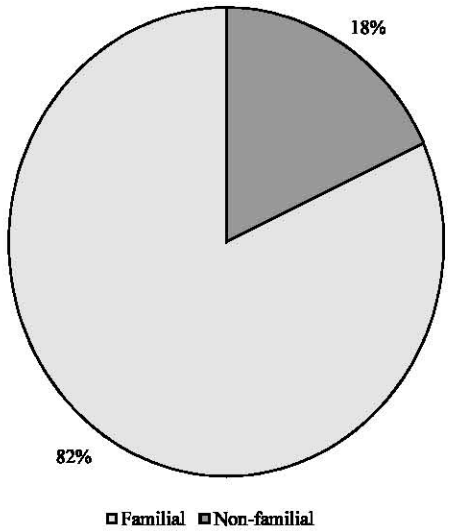

Fig. 4: Familial incidence

the age group of 11-20 (29.4%) followed by 1-10 (25%) years. It was observed that, in the later age groups, as there is an increase in the age of onset, there is a decrease in the incidence of the vitiligo patients. The mean age of onset of pooled data (3551 vitiligo patients) was reported as 22.86±15.48 further, the mean age of males and females was 24.73±15.32; 20.46±15.34, respectively. The mean age of onset of disease in different classes is given in Table 1.

The overall sex ratio of the patients for male to female was found to be 55:45%, which is highly significant with a chi-square value of 34.57 ($p<0.05$). Out of five groups of vitiligo, non-dermatomal, dermatomal and focal vitiligo showed male to female sex ratio of 1:1. However, mucosal and acrofacial groups have exhibited male preponderance and sex ratio was observed to be 2:1 that has a statistically significant difference (chi-square value 39.189 at $p<0.05$) which indicates gender related variation (Fig. 3). There is an significant association between type of vitiligo and gender even after adjusting the age at onset using mixed model analysis. The pooled data has shown that overall 18% (638) of the patients are reported to be with a family history of vitiligo (Fig. 4).

DISCUSSION

Vitiligo is a heterogeneous group of disorder characterized by variation in clinical manifestation, disease course and probably response to therapeutic intervention. The disease is characterized by incomplete penetrance, multiple susceptible loci and genetic heterogeneity. Hence, genetics of vitiligo cannot be explained on the basis of simple Mendelian pattern. Although environmental factors are important, twin and family studies have given considerable evidence that genes play a significant role in the pathogenesis of vitiligo (Zhang *et al*., 2005). Further, familial cases of vitiligo are common indicating a hereditary factor. Earlier studies showed that between 6 and 38% of vitiligo patients have family members with vitiligo. Present study reveals that 18% of patients show family history of vitiligo, which is in accordance to the earlier study from India (Virendra and Srivastava, 2007).

Probably, to our knowledge, this is the first report to show gender based variation with male preponderance with respect to vitiligo. Number of reports from various populations like Egyptians (Anbar *et al*., 2006) Kuwaith (Nawaf and Ashok, 2006; Hann *et al*., 1997) Korean (Bang *et al*., 2000), Nigerian, Africans (Onunu and Kubeyinje, 2003) and from India (Behl *et al*., 1999; Tawade *et al*., 1997) did not exhibit significant gender variation, except one report from India in children where the sample size is quite small (Jaisankar *et al*., 1992).

In order to understand the gender variation in the pooled data, we followed the classification where patients are classified based on the clinical symptoms into 5 different classes such as non-dermatomal (class I), dermatomal (class II), mucosal (class III), acrofacial (class IV) and focal (class V). The analysis exhibited interesting results where class I, II and V showed at about 1:1 (male: female ratio), where as classes III and IV showed 2:1 ratio ($p<0.05$) indicating that the contributors of gender variation to pooled data comes from class III and IV (Fig. 3). This prompted us to assume that variation in etiological/pathophysiological factors must be the basis for clinical variants.

The genetic marker analysis in different ethnic groups has suggested locus heterogeneity involving 4q, 1p, 7q, 8p, 17p, 6p, 6q, 14q, 9q, 13q and 22q chromosomal locations (Zhang *et al*., 2005) and a number of candidate genes have been suggested to mediate susceptibility including AIRE, CTLA4, GCH1, VIT1, MHC, CAT, COMT and SLEV1 (Pamela *et al*., 2003; Richard *et al*., 2004; Jian *et al*., 2005). However, overlapping is not 100% with respect to loci in different ethnic groups. Apart from this, the genome wide analysis carried out by various study groups did not considered the X-chromosome markers, as significant gender variation was not observed by most of the study groups. Indirect support for this hypothesis of involvement of X-chromosome gene(s) comes from literature available on G6PDH levels in vitiligo patients (Agarwal *et al*., 2004; Shajil and Begum, 2006). Further studies by Saha *et al*. (1982) demonstrated significantly reduced levels of this enzyme in vitiligo patients. In the present analysis, an attempt was made to explain gender variation observed in this study on the basis of involvement of X-linked genes.

According to Seli and Arici (2002) autoimmune diseases with female preponderance is suggestive of TH2 type of immunological mediation (Hashimato thyroidites, SLE, Graves diseases) and male preponderance is suggestive of TH1 (Rheumatoid arthritis, Multiple sclerosis, Type 1 insulin dependent diabetes mellitus (Seli and Arici, 2002). An autosomal gene CTLA4 is implicated in vitiligo is associated with a number of dysregulatory autoimmune diseases (Kemp *et al*., 1999; Blomhoff *et al*., 2005).

However, controversial report regarding CTLA4 polymorphism in vitiligo may suggestive of the involvement of other immuno-regulatory genes (Javed *et al*., 2005). In the present study, mucosal and acrofacial type of vitiligo represent significantly more number of male patients compared to females and also higher mean age of onset generally a feature of autoimmune diseases (Dogra *et al*., 2005). Higher mean age and male preponderance in these two groups may suggest differences in etiology/pathophysiology of these two classes compared to others classes of vitiligo. In this connection, it is proposed that major/minor X-linked gene(s) may be involved in subtypes of vitiligo along with autosomal loci. So, far the genome wide analysis carried out by various study groups did not consider the X-chromosomal markers, as significant gender variation was not observed by most of these groups (Pamela *et al*., 2003; Richard *et al*., 2004; Jian *et al*., 2005).

Understanding the differences among various kinds of vitiligo is important for gene mapping, drug response variation and the outcome of treatment. In order to test the present hypothesis, markers from X-chromosome are suggested to be included in the genome wide analysis and large families of different clinical variants with high penetrance to be studied.

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