Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 02, 2023

ORIGINAL RESEARCH

Association of 511 C/T Polymorphism of Interlukin 18 Gene Along with Prevalence of C/T Allele of Il1b Gene in Case and Controls of Vitiligo

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Received Date: 14/01/2023 Acceptance Date: 10/03/2023

ABSTRACT

Background: Vitiligo is characterized by a disappearance of epidermal and/or follicular melanocytes which result in pale white patches on skin. It is an autoimmune disease and can develop at any age and in any gender. People affected by vitiligo can experience low self-esteem and concern about their appearance, leading to disturbed mental state and thereby affecting the quality of life. Methodology- The study was conducted at Sri Aurobindo Medical College and Post Graduate Institute, Indore, Central Research Laboratory and Department of Skin and VD, from Oct 2014 to April 2016. 84 patients who were known case of vitiligo were enrolled for the study. Written informed written consent was taken from all the patients. Detailed clinicalexamination was done on all patients to rule out other systemic disorders. 5ml of blood samples were collected in plain and EDTA tube from peripheral veins under aseptic precautions. Serum was separated by centrifugation of plain tube at 2000rpm.DNA isolation process was done.Results- The frequency of CC, CT and TT genotype of IL1b gene in our study was 27.4%, 48.8% and 23.8% cases and that were in controls were 28.8%, 43.8% and 27.4% respectively. Conclusion- No significant association of Il1b -511C/T polymorphism at genotype level was seenwith the vitiligo.

Keywords-Interlukin18, vitiligo, gene, skin, melanocyte.

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INTRODUCTION

Vitiligo denotes an acquired, primary, usually progressive, melanocytopenia of unknown etiology,clinically manifested by circumscribed achromic macules often associated with leukotrichia and histologically by degeneration and disappearance of melanocytes in the involved skin and not infrequently in the pigment epithelium of the eyes, leptomeninges and

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 02, 2023

inner ear.1The population prevalence of vitiligo ranges from 0.1% to 2% and shows a wide variability among ethnic groups.2,3 In India, its incidence ranges from 0.1 to > 8.8% across the country.4-6 Adults and children of both sexes are equally affected although the greater number of reports among femalesis probably due to the greater social consequences to women and girls affected by this condition.7The proportion of patients with positive family history vary from one part of the worldto another. In India, in particular, it ranges from 6.25-18%. In some studies, it is as high as 40%. 8,9The mode of transmission of vitiligo is quite complex. Vitiligo is characterized by the appearance of patchy discoloration evident in the form of typical chalky-white or milky macule(s).The macules are round and/or oval in shape, often with scalloped margins. The size of the maculesmay vary from a few millimeters to several centimeters with the lesions affecting the skin and/or mucous membranes. By and large, the lesions are asymptomatic although itching / burning may precede or accompany the onset of the lesions in a few patients.10,11 Vitiligo is a slow, progressivedisease and may have remissions and exacerbations correlating with triggering events. Occasionally, the lesions of vitiligo may begin to form around a pigmented nevus (Sutton's nevus,leukoderma aquisitum centrifugum) and then go on to affect distant regions.12Common sites of involvement include 'the external body surfaces such as the pretibial region, sides of ankles, knees,elbows, and skin overlying the digits, periorificial areas such as the periocular, circumoral and anogenital areas (glans penis, prepuce, and vulva) and also the flexor aspect of the wrists, axillae,groin, lower back and loin, palms, soles, toe tips, finger tips and scalp. The pretibial site is most commonly affected site in India.13 Palmar and plantar involvements is also quite common in India.14It is also believed that vitiligo has an autoimmune basis.15 Vitiligo itself is a component ofthe APECED (APS1) and Schmidt (APS2) multiple autoimmunity syndromes.16 A number of studies have suggested the association of vitiligo with other autoimmune diseases, including thyroid disease.17,18 pernicious anaemia 19-21, diabetes mellitus22, alopecia areata23, and Addison's disease 24-25.

IL-1beta is located on Chromosome 2 at location 113,303,808-113,310,827. It is located in the middle of IL-1a and IL1-RN between 40 and 110kb from IL-1a. The pro IL-1β gene is composedof seven exons with a primary transcription product length of 7,008 nucleotides.26 Recently, Laddha et al shows that NPY 2399T/C, +1128T/C and IL1B 2511C/T polymorphisms areassociated with vitiligo and IL1B 2511C/T SNP influences its transcript levels leading to increased risk for vitiligo.27 IL1B induces biosynthesis and release of Neuropeptide-Y which in turn induces the catecholamine release.28 Abnormal release of catecholamines from autonomic nerve endings may play an etiological role in the onset and development of vitiligo by an over production of toxicradicals in the microenvironment of melanocytes.29

Therefore, the present study is designed to study the association of 511 C/T polymorphism of Interlukin 18 gene alongwith prevalence of C/T allele of IL1B gene in case and control of vitiligo.

MATERIALS & METHODS

This prospective case control study was conducted at Sri Aurobindo Medical College and Post Graduate Institute, Indore, Central Research Laboratory and Department of Skin and VD, during Oct 2014 to April 2016. All the necessary ethical permissions were taken from the Institutional Ethics Committee. 84 known patients of vitiligo were recruited for the study. Patients were diagnosed to have vitiligo based on history, duration, progression of disease presence of depigmented patch and appearance of chalky white on wood's lamp examination. 76 healthy controls were also recruited for comparative analysis. Written informed consent was taken from all the patients. Detailed clinical examination was done on all patients to rule out other systemic disorders. Patients were diagnosed to have vitiligo based on history,

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 02, 2023

duration, progression of disease presence of depigmented patch and appearance of chalky white on wood's lamp examination.

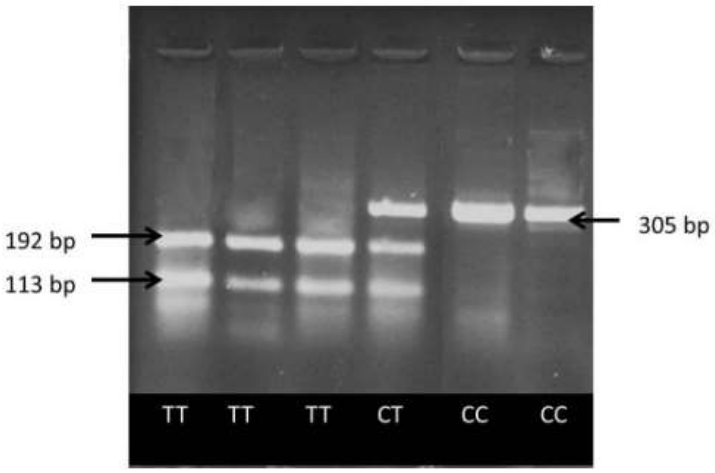
INCLUSION CRITERIA

Vitiligo patients of both sexes and any age group were included.
All types of vitiligo were included in the study.

EXCLUSION CRITERIA

Patients with other pigmentary disorders like Lichen sclerosus et, Nevus depigmentosis, Nevus anaemicus, Halo nevus, Leprosy, Incontenenti pigmenti, leucoderma, Post-inflammatory hypopigmentation, Idiopathic guttate hypomelanosis, pityriasis versicolor, albinism.

History was taken regarding any present illness, past history of vitiligo and other systemic disorders, past medical history, family history. Patients' general examination was done regardingpallor, icterus, clubbing, oedema, and lymphadenopathy were checked and recorded in all patients.Wood's Lamp examination was done in patients to see the appearance of chalky white. DNA isolation was done. Polymerase chain reaction method was used for genotyping the IL1B -511C/TSNP, followed by restriction fragment length polymorphism (PCR-RFLP) method.



Statistical Analysis:

Data was entered in Microsoft excel and analysed on Graph Pad Software (demo version). Chi Square test was applied to see the difference in qualitative variables in two groups. a P-value lessthan 0.05 was considered significant.

RESULT

A total of 84 vitiligo patients were included in the study. For comparison of results 74 age and sexmatched healthy individuals were also recruited as a control. Graph.1 shows that maximum (26) cases and controls (30) were in between age group 21-30 years. and minimum (7) cases were present in each 0-10 year and 40-50 years of age group. There was no significant difference in agein cases and controls (P =0.132).

There were 45 males in cases and 48 in controls and 39 females in cases and 25 in controls. No significant difference in frequencies of different gender was seen in cases and controls (P= 0.121)(Graph.2)

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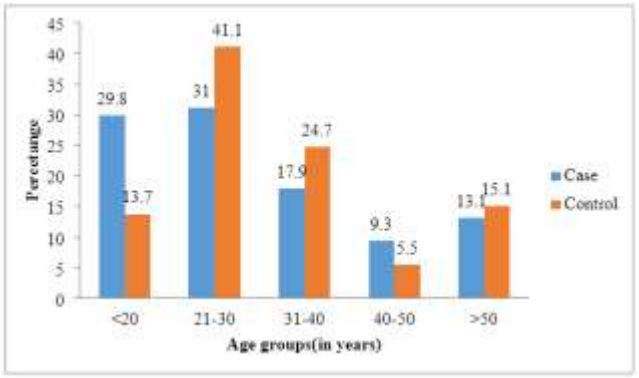
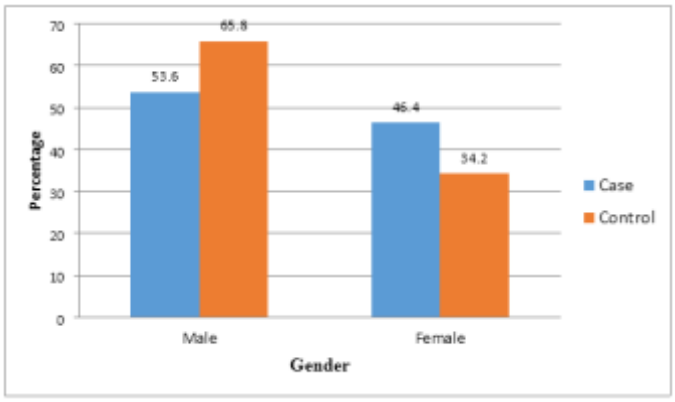


Graph 1



Graph 2

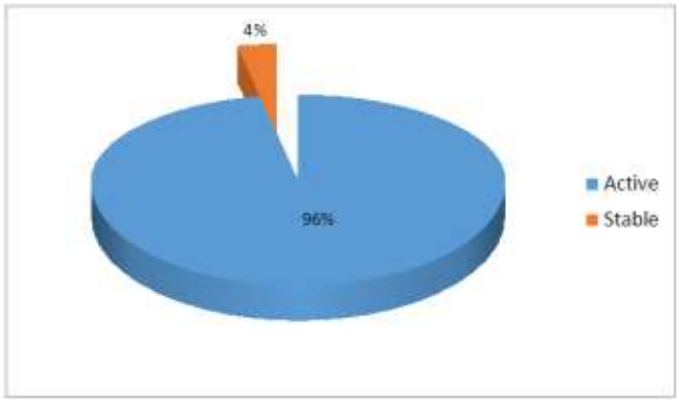


Figure 1

Active type of vitiligo was observed in 82 patients and 2 were stable (Fig.1).

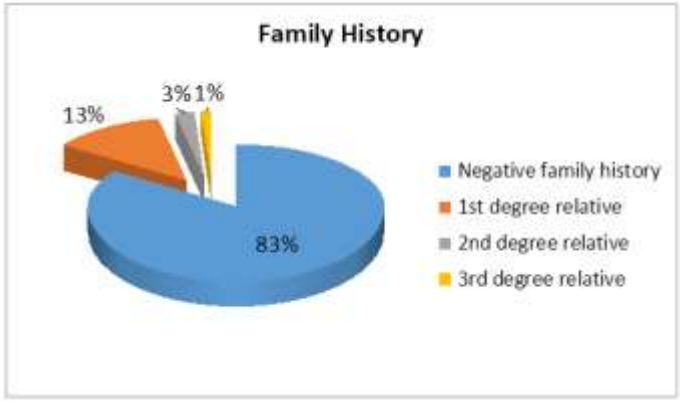


Figure 2

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There was a family history of vitiligo in 14 cases. None of the controls had a family history ofVitiligo. (Fig.2)

TABLE 1: Interleukin 1B Genotype frequency

	Case	Control	Total
CC	23 (27.4)	21 (28.8)	49 (28)
CT	41 (48.8)	32 (43.8)	73 (46.5)
TT	20 (23.8)	20 (27.4)	40 (25.5)

P= 0.806

CC genotype of IL1b gene was present in 23 cases and 21 controls whereas TT genotype was present in 20 cases and 20 controls. No significant association of Il1b -511C/T polymorphism at genotype level was seen with the vitiligo.

DISCUSSION

This prospective case control study was done in the Central Research Laboratory and Department of Skin and VD, Sri Aurobindo Medical College and Post Graduate Institute of Medical Sciences, Indore. In this study role of Interleukin 1B -511 C/T polymorphism in vitiligowas studied. Younger people were more frequently affected and had active vitiligo compared to older people. In present study most of the cases were in the 2nd and 3rd decade which is similar to study done by Shah et al**30**, Kumar et al**6**, Martis et al**31**, Fatani et al**32** and Vora et al.**33**

Table 2: Age groups of vitiligo patients in different studies

Age groups (in Year)	**Present study**	**Fatani et al**	**Shah et al**	**Vora et al**	**Kumar et al**
0-10	9.3	24.4	21.64	20.8	6.5
11-20	21.4	27.4	32.87	27.0	26.08
21-30	31.0	17.8	15.61	21.9	21.7
31-40	17.9	9.6	14.52	14.2	21.7
41-50	9.3	9.6	9.86	16.1	15.2
>50	13.1	11.1	5.47	-	8.7

The male to female ratio in present study was 1.15: 1 showing males and females were affected with almost equal frequency. Our study was similar to previous reports of Martis et al**31**, Koranneet al**34**, Shankar et al**35**, Misri et al**36**, Reghu et al**37**, Mchepange et al.**38** However Handa et al**5**, Sarinet al**39** and Khaitan et al**40** showed, male was more commonly affected than female. Higher femaleto male ratio was reported by Shajil et al**8** and Kumar et al**6**.

Table 3: Family history of vitiligo

parameters	**Our study**	**Fatani et al**	**Singh et al**	**Behl et al**
Family history	14(16.66%)	26(19.25%)	44(22%)	8.4%
1st degree relative	11(13.09%)	20(19%)	26(13%)	4.8%
2nd degree relative	2(2.38%)	5(4.8%)	11(5.5%)	2.9%
3rd degreerelative	1(1.19%)	1(1%)	7(3.5%)	0.86%

Familial occurrence has been reported to vary from 5 to 30% in different studies**8**,**10**. In present study family history was observed in 8.3% of cases. Vora et al**32** from Gujarat reported a higher incidence of family history of 20.4%. Koranne et al**34** stated that in India, family history ranged from 6.25% to 18%. Similar to our study, Fatani et.al**32**, Singh et.al**41** and Behl et.al**42** reported

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 02, 2023

the 1st degree relative more affected as compared to 2nd and 3rd degree relatives in patient who had family history.
The frequency of CC, CT and TT genotype of IL1b gene in our study was 27.4%, 48.8% and 23.8% cases and that were in controls were 28.8%, 43.8% and 27.4% respectively.
Laddha et al**27** reported the frequency of CC, CT and TT genotype of IL-1B gene in their study as52%, 35% and 13% cases and that were in controls as 62%, 0.34% and 0.03% respectively. Therewas no significant association of Il1b -511C/T polymorphism at genotype level and allele level with the vitiligo in our study.

LIMITATION OF STUDY

The sample size in our study was small to analyse the proper results. In our study the frequencyof localised and stable vitiligo was very less.

CONCLUSION

The frequency of CC, CT and TT genotype of IL1b gene in our study was 27.4%, 48.8% and 23.8% cases. There was no significant association of Il1b -511C/T polymorphism at genotype level and allele level with the vitiligo in this study.

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