Association of Cytotoxic T lymphocyte antigen-4 (CTLA4) gene variants with nondermatomal vitiligo

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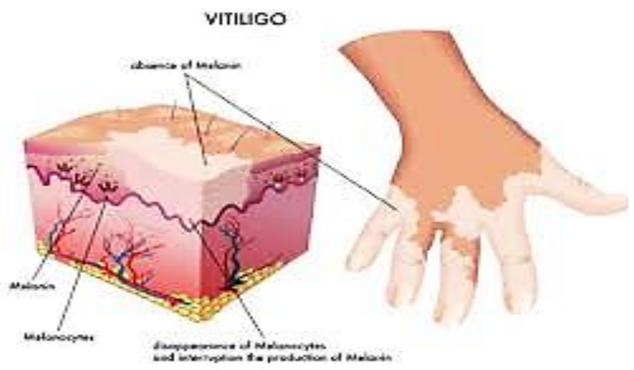
Introduction

- Vitiligo is an acquired depigmentation disorder affecting 0.5–4% of the world's population and 0.1% to >8.8% in India.
- There are different hypothesis involving Oxidative stress, self destruction, immune hypothesis and also including he genetic component to explain the pathogenesis of vitiligo.
- Accumulating evidence has demonstrated that a series of complex autoimmune responses, particularly cellular immunity-related responses resulting in melanocyte damage, plays a major role in vitiligo.

Vitiligo: Autoimmune destruction of melanocytes



Genetic relations of generalized vitiligo susceptible genes and other autoimmune diseases

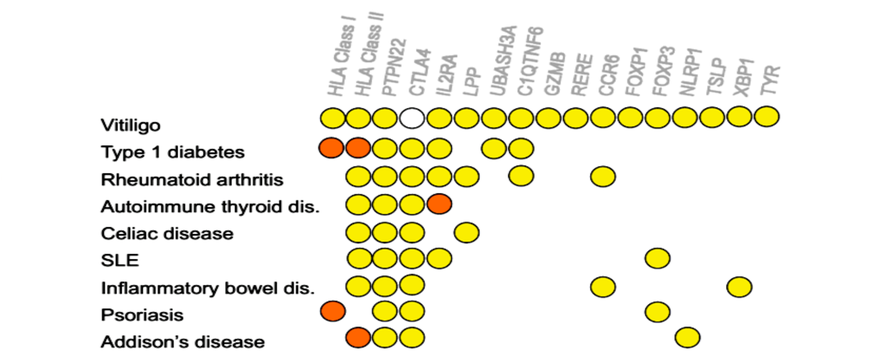
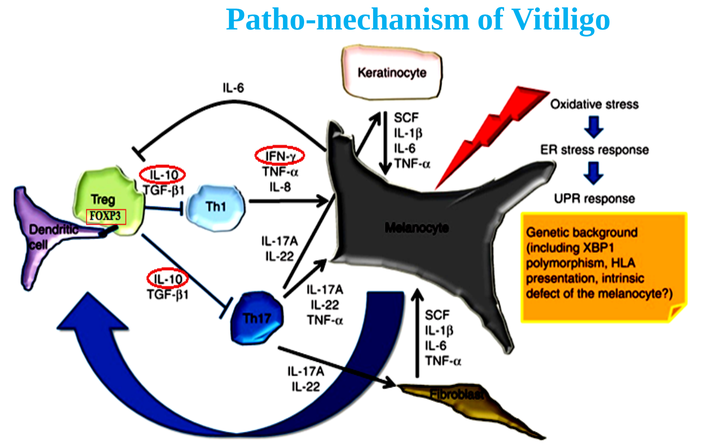


Figure 2. Genetic relationships of generalized vitiligo susceptibility genes and other autoimmune diseases. Circles indicate loci associated with susceptibility to a given autoimmune disease: yellow, shared risk alleles; orange, opposite risk alleles at same SNP; white, secondary association due to primary association with autoimmune disease epidemiologically associated with generalized vitiligo. SLE, systemic lupus erythematosus.

Patho-mechanism of Vitiligo



Cytotoxic T lymphocyte antigen (CTLA-4)

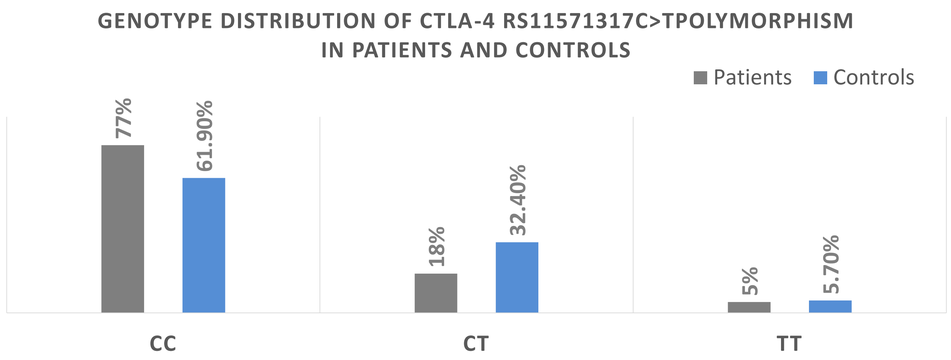
The Cytotoxic T lymphocyte antigen (CTLA-4) gene having the role of T cell cytotoxicity is mapped to chromosome 2q33. CTLA4 is also recognized as CD152 a co-stimulatory molecule present on activated T lymphocytes and is important regulator of CD 4 T cell responses. The *CTLA4* gene encodes cytotoxic T lymphocyte antigen 4, a key negative feedback regulator of T-cell activation and proliferation during the immune response . Variation in *CTLA4* has been genetically associated with a number of autoimmune diseases including vitiligo, an acquired pigmentary disorder resulting from loss of melanocytes. However, studies of genetic association between *CTLA4* and vitiligo have yielded conflicting results.

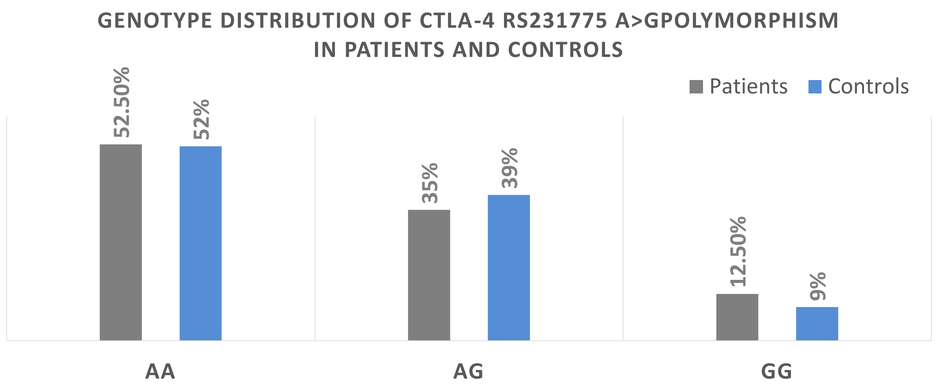
Aim of the study

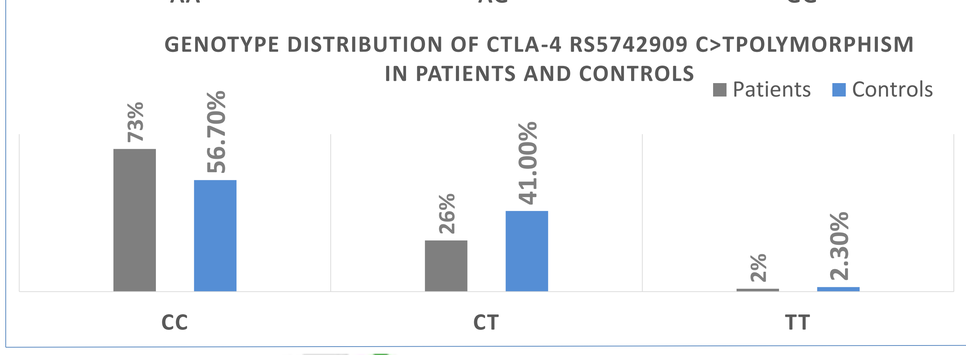
The present study is aimed at investigating the role of functional polymorphisms of CTLA-4 gene (rs11571317 C>T, rs231775 A>G and rs5742909 C>T) in susceptibility to vitiligo.

Methodology

- Genotyping was performed by PCR-RFLP and ARMS-PCR in a total of 410 subjects (200 vitiligo patients and 210 normal healthy controls). Data was subjected to appropriate statistics. Hyderabad.
- An inclusion criterion of patients was the presence of Nondermatomal vitiligo without any other disorders
- The Exclusion criteria were Segmental or non active vitiligo, Patients with known allergies, Patients with other skin disease, Presence of any other autoimmune disorder..







Results

Haplotype association with response (n=410, adjusted by Gender)						
	rs11571317	rs231775	rs5742909	Freq	OR (95% CI)	P-value
1	C	A	C	0.5486	1.00	---
2	C	G	C	0.1282	1.72 (1.04 - 2.86)	0.036
3	C	A	T	0.0973	0.42 (0.23 - 0.78)	0.0059
4	T	G	C	0.0801	0.48 (0.26 - 0.88)	0.018
5	T	A	C	0.0553	0.58 (0.29 - 1.16)	0.13
6	C	G	T	0.0454	0.49 (0.20 - 1.20)	0.12
7	T	G	T	0.0402	0.89 (0.37 - 2.14)	0.79
rare	*	*	*	0.0049	0.00 (-Inf - Inf)	1
Global haplotype association p-value: 0.00019						

Multifactor dimensionality reduction analysis

No of Loci	Gene variants in each model	CV	Testing Accuracy	Training Accuracy	χ^2 (p value)	OR
1	X3	6/10	0.544	0.581	10.87(P=0.0001)	2.09 (1.34-3.25)
2	X1,X3	10/10	0.6265	0.6265	23.64(<0.0001)	2.81 (1.84-4.29)
3	X1,X2,X3	10/10	0.60	0.6424	30.64(<0.0001)	3.34 (2.16-5.17)

Conclusion Our findings suggest the role of CTLA-4 in the vitiligo pathogenesis and for the first time we report the association of rs11571317 and rs5742909 polymorphisms in relation to vitiligo.

Acknowledgements

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