

# Association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism and susceptibility to vitiligo: Systematic review and meta-analysis

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## Abstract

**Background:** Protein tyrosine phosphatase, non-receptor type 22 gene, which translates to lymphoid tyrosine phosphatase, is considered to be a susceptibility gene marker associated with several autoimmune diseases. Several studies have demonstrated the association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism with vitiligo. However, these studies showed conflicting results. Meta-analysis of the same was conducted earlier that included fewer number of publications in their study.

**Aim:** We performed a meta-analysis of a total of seven studies consisting of 2094 cases and 3613 controls to evaluate the possible association of protein tyrosine phosphatase, non-receptor type 22 +1858C>T polymorphism with vitiligo susceptibility.

**Methods:** We conducted a literature search in PubMed, Google Scholar and Dogpile for all published paper on protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism and vitiligo risk till June 2016. Data analysis was performed by RevMan 5.3 and comprehensive meta-analysis v3.0 software.

**Results:** Meta-analysis showed an overall significant association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism with vitiligo in all models (allelic model [T vs. C]: odds ratio = 1.50, 95% confidence interval [1.32–1.71],  $P < 0.001$ ; dominant model [TT + CT vs. CC]: odds ratio = 1.61, 95% confidence interval [1.16–2.24],  $P = 0.004$ ; recessive model [TT vs. CT + CC]: odds ratio = 4.82, 95% confidence interval [1.11–20.92],  $P = 0.04$ ; homozygous model [TT vs. CC]: odds ratio = 5.34, 95% confidence interval [1.23–23.24],  $P = 0.03$ ; co-dominant model [CT vs. CC]: odds ratio = 1.52, 95% confidence interval [1.09–2.13],  $P = 0.01$ ). No publication bias was detected in the funnel plot study.

**Limitations:** Limited ethnic-based studies, unable to satisfy data by gender or vitiligo-type are some limitations of the present meta-analysis.

**Conclusion:** Stratifying data by ethnicity showed an association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T with vitiligo in European population (odds ratio = 1.53, 95% confidence interval [1.34–1.75],  $P < 0.001$ ) but not in Asian population (odds ratio = 0.59, 95% confidence interval [0.26–1.32],  $P = 0.2$ ). In conclusion, protein tyrosine phosphatase, non-receptor type 22 +1858 T allele predisposes European individuals to vitiligo.

**Key words:** Meta-analysis, protein tyrosine phosphatase, non-receptor type 22, rs2476601, vitiligo

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## Introduction

Vitiligo is a hypomelanotic dermatologic disorder on the skin that may gradually enlarge and appear anywhere on the body.<sup>1,2</sup> It is caused by the destruction of functional melanocytes resulting in melanin loss from the lesion site. The etiology of melanocyte destruction has not been fully understood, but intricate interactions of environmental triggers, genetics, alteration in biochemical factors and immunological factors are thought to be involved in its pathogenesis.<sup>3</sup> Various hypotheses have been proposed, of which autoimmunity has been suggested to be playing a pivotal role in its pathogenesis. Epidemiological studies have reported the presence of autoantibodies against melanosomal proteins such as tyrosinase,<sup>4</sup> gp100/pmel17,<sup>5</sup> tyrosinase-related protein (tyrosinase-related protein 1 and tyrosinase-related protein 2)<sup>6</sup> in the serum and autoreactive cytotoxic T-cell lymphocytes in peripheral blood and perilesional skin of vitiligo patients,<sup>7</sup> which supports the autoimmunity theory of vitiligo. The autoimmune hypothesis is also supported because of the association of vitiligo with other autoimmune diseases such as rheumatoid arthritis, type 1 diabetes mellitus, pernicious anemia, autoimmune thyroid disease, Addison's disease and systemic lupus erythematosus.<sup>8-10</sup> Interaction between genetic and environmental factors influences the development of autoimmune disease. Linkage and association studies have been conducted through which many genes such as major histocompatibility complex, cytotoxic T-lymphocyte antigen 4, human leukocyte antigen, NALP1, protein tyrosine phosphatase, non-receptor type 22 and autoimmune regulator 1, liver X receptor- $\alpha$  gene have been implicated in the pathogenesis of vitiligo.<sup>1,11,12</sup> Among these, protein tyrosine phosphatase, non-receptor type 22 (lymphoid-specific) locus is considered to be one of the strongest risk factors associated with autoimmune disease.<sup>13</sup> Protein tyrosine phosphatase, non-receptor type 22 gene located on chromosome 1p13.2-p13.1 codes for an intracellular protein named lymphoid-specific tyrosine phosphatase. Lymphoid-specific tyrosine phosphatase protein plays a crucial role in the negative regulation of T-cell antigen receptor signaling pathway.<sup>14</sup> Lymphoid-specific tyrosine phosphatase binds with the Src homology 3 domain of the C-terminal Src kinase forming a complex which inhibits the T cell receptor-signaling and ultimately inhibits T cell development and activation.<sup>15</sup> Protein tyrosine phosphatase, non-receptor type 22 gene maintains the central and peripheral tolerance in the body. Polymorphic change in protein tyrosine phosphatase, non-receptor type 22 at nucleotide position +1858 from C to T has shown to disrupt the function of protein tyrosine phosphatase, non-receptor type 22 which may predispose a person to autoimmune disease. Protein tyrosine phosphatase, non-receptor type 22 +1858C→T single-nucleotide polymorphism is a missense/nonsynonymous single-nucleotide polymorphism, in which change in the amino acid at position 620 from an arginine to tryptophan is observed (R620W). This change disrupts the interaction between lymphoid tyrosine phosphatase and C-terminal Src kinase which downregulates the T-cell antigen receptor-signaling threshold. Thus, T-cell activation occurs in an uncontrollable fashion and may become a cause in the development of autoimmune disease.<sup>13,15</sup> Protein tyrosine phosphatase, nonreceptor type 22 +1858C→T single-nucleotide polymorphism, first introduced by Mustelin's group,<sup>16</sup> has been associated with several autoimmune diseases such as type 1 diabetes mellitus,<sup>16</sup> Graves' disease,<sup>17</sup> systemic lupus erythematosus,<sup>18</sup> rheumatoid arthritis,<sup>19</sup> myasthenia gravis and<sup>20</sup> Addison's disease.<sup>21</sup>

Several studies were conducted to explore the association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T

and vitiligo susceptibility, but it still remains unclear because of inconsistent and inconclusive results from different studies.<sup>8,22-27</sup> This inconsistency may be due to inadequate statistical power, racial and ethnic differences, small sample size or other limitations. Meta-analysis of pooled data from different studies has been proven useful to assess an overall risk of a polymorphism with the disease susceptibility. Hence, we performed a meta-analysis of all available studies to clarify and to provide comprehensive assessment of the association between protein tyrosine phosphatase, non-receptor type 22 +1858C→T (rs2476601) and vitiligo susceptibility.

## Methods

### Strategy for literature search

To identify all articles that examined the association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism with vitiligo susceptibility, we conducted a literature search in PubMed, Google Scholar and Dogpile for all the published paper assessing the association between protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism and vitiligo risk using the following terms and keywords: "Protein tyrosine phosphatase, non-receptor type 22," "protein tyrosine phosphatase, non-receptor type 22 1858C→T," "rs2476601" and vitiligo. The last search updated to June 2016. Additional eligible studies were identified by a manual search of references cited in selected studies and previously published review articles on this topic.

### Inclusion and exclusion criteria

Studies were considered to be eligible only when they meet the following inclusion criteria: (1) Study must be evaluating the association between protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism and vitiligo risk, (2) only case-control design studies were selected without gender bias, (3) study must have sufficient published data available such as sample size, genotype distribution or allelic frequencies for both cases and control for estimating the odds ratio with its 95% confidence interval, (4) genotype distribution of control group must be consistent with Hardy-Weinberg equilibrium and (5) family-based studies were excluded.

### Data extraction

From each eligible study following data were extracted: First author's name, publication year, country of origin, ethnicity and genotyping distribution for the gene protein tyrosine phosphatase, nonreceptor type 22 in cases and control and *P* value of Hardy-Weinberg equilibrium. The genotype distribution for the gene polymorphism protein tyrosine phosphatase, nonreceptor type 22 +1858C→T in cases and control for each study is extracted for statistical analysis.

### Statistical analysis

The strength of the association between protein tyrosine phosphatase, nonreceptor type 22 +1858C→T polymorphism and vitiligo risk was estimated by calculating pooled odds ratio and 95% confidence interval whose significance was determined by *Z*-test ( $P < 0.05$  was considered statistically significant). The pooled odds ratios and 95% confidence intervals were calculated for the following genotypic models: Allelic model (T vs. C), homozygote model (TT vs. CC), dominant model (CT + TT vs. CC), recessive model (TT vs. CT + CC) and codominant model (CT vs. CC).

Heterogeneity test (Chi-square-based *Q*-test and *I*<sub>2</sub>-test) was performed to test the heterogeneity between studies which helps in

selecting the appropriate model (random effect model or fixed effect model) to calculate the pooled effect estimate.<sup>28</sup> The Q-statistic tests with  $P < 0.10$  or  $I_2 > 50\%$  defined as the presence of a significant degree of heterogeneity between studies. For  $P > 0.10$  or  $I_2 < 50\%$ , fixed-effect model<sup>29</sup> was used; otherwise, random-effect model<sup>30</sup> was used to calculate the pooled effect. Sensitivity analysis was tested to study the effect of each study on the overall meta-analysis result and thus to conclude about the stability of meta-analysis results. The potential publication bias was estimated by visual inspection of the funnel plot along with the  $P$  value obtained by Begg's test and Egger's linear regression test.  $P < 0.05$  was considered as the existence of statistically significant publication bias. All statistical tests were performed with software RevMan v5.3 (The Nordic Cochrane Centre, Copenhagen) and comprehensive meta-analysis v3.0.

**Results**

To assess the possible association of protein tyrosine phosphatase, nonreceptor type 22 +1858C>T polymorphism with vitiligo susceptibility, meta-analysis was done by combining all the available studies which fulfilled the inclusion criteria.

**Search results and study characteristics**

We identified 162 articles, out of which seven studies with total 2094 vitiligo patients and 3613 controls fulfilled the inclusion criteria and were included in this meta-analysis [Figure 1]. Baseline characteristics and genotype distribution of included studies are shown in Table 1. The genotype distributions in controls in each study were consistent with Hardy–Weinberg Equilibrium.

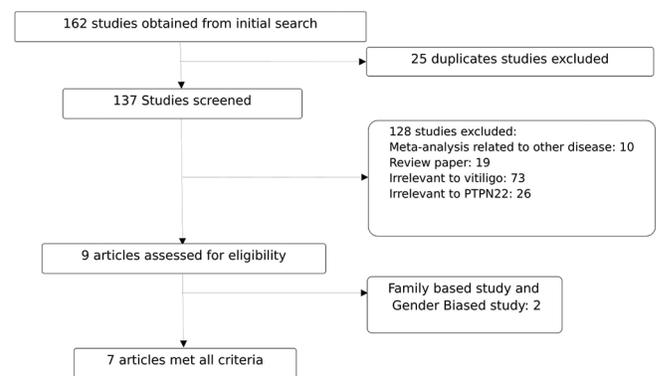
**Meta-analysis results**

The pooled statistical results of meta-analysis of all the seven included studies to estimate the association of protein tyrosine phosphatase, nonreceptor type 22 +1858C→T with vitiligo risk are shown in Table 2. No significant heterogeneity between the studies was found ( $P > 0.1$ ,  $I^2 < 50\%$ ); therefore, fixed effect model was used to calculate the pooled estimate. We found an overall significant association between the protein tyrosine phosphatase, nonreceptor type 22 +1858C→T and vitiligo risk under: Allelic model (1.50,

95% confidence interval [1.32–1.71]  $Z = 6.61$ ,  $P < 0.001$ ), dominant model (1.61, 95% confidence interval [1.16–2.24]  $Z = 2.84$ ,  $P = 0.004$ ), recessive model (4.82, 95% confidence interval [1.11–20.92]  $Z = 2.10$ ,  $P = 0.04$ ), homozygote model (5.34, 95% confidence interval [1.23–23.24]  $Z = 2.23$ ,  $P = 0.03$ ) while there was no significant association for codominant model (1.52, 95% confidence interval [1.09–2.13]  $Z = 2.45$ ,  $P = 0.01$ ) [Figure 2a-e]. In subgroup analysis stratified by ethnicity, we found a significant association between protein tyrosine phosphatase, nonreceptor type 22 +1858C→T and vitiligo risk in European population (1.53, 95% confidence interval [1.34–1.75]  $Z = 6.24$ ,  $P < 0.001$ ) but not with Asian (0.59, 95% confidence interval [0.26–1.32]  $Z = 1.28$ ,  $P = 0.2$ ) [Figure 3a and b].

**Sensitivity analysis and publication bias**

Odds ratio and corresponding 95% confidence interval were not significantly altered after removing each study which confirms the stability of meta-analysis results. There was a lack of publication bias as shown by symmetry of inverted funnel plot [Figure 4]. To confirm publication bias, both Begg's test and Egger's regression test were performed.  $P$  values for both tests support no existence of publication bias under the models: Allelic (Begg's  $P = 0.45$ , Egger's



**Figure 1:** Flow chart of literature search, inclusion and exclusion criteria for meta-analysis

**Table 1: Baseline characteristics and genotypes distribution of included studies**

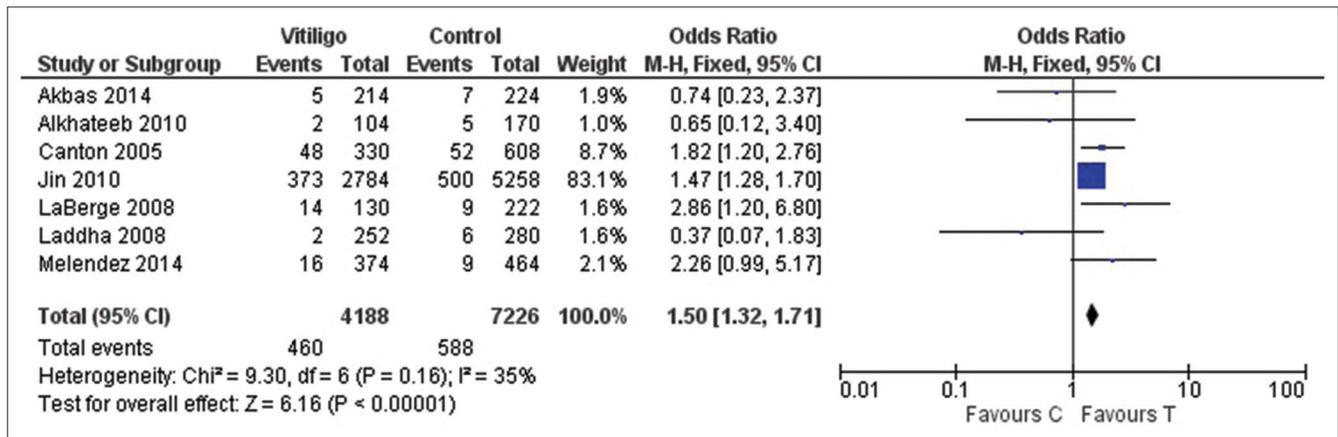
Author	Year	Country	Ethnicity	Genotype method	Patient number	Control number	Vitiligo			Control			P value for HWE				
							CC	CT	TT	CC	CT	TT		C	T	C	T
Akbas <i>et al.</i>	2014	Turkey	Asian	PCR-RFLP	107	112	102	5	0	105	7	0	209	5	217	7	0.73
Alkhateeb <i>et al.</i>	2010	Jordan	Asian	PCR-RFLP	52	85	50	2	0	80	5	0	102	2	165	5	0.78
Canton <i>et al.</i>	2005	UK	European	PCR-RFLP	165	304	122	38	5	254	48	2	282	48	556	52	0.87
Jin <i>et al.</i>	2010	UK	European	Genome-wide association	1392	2629							2411	373	4758	500	
Laberge <i>et al.</i>	2008	USA	European	PCR-RFLP	65	111	52	12	1	102	9	0	116	14	213	9	0.65
Laddha <i>et al.</i>	2008	India	Asian	PCR-RFLP	126	140	124	2	0	134	6	0	250	2	274	6	0.79
Melendez <i>et al.</i>	2014	Mexico	Mexican	PCR-RFLP	187	232	171	16	0	223	9	0	358	16	455	9	0.76
Total					2094	3613	0.89	0.11	0.008	0.91	0.09	0.002	0.89	0.11	0.92	0.08	

HWE: Hardy-Weinberg equilibrium, PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism

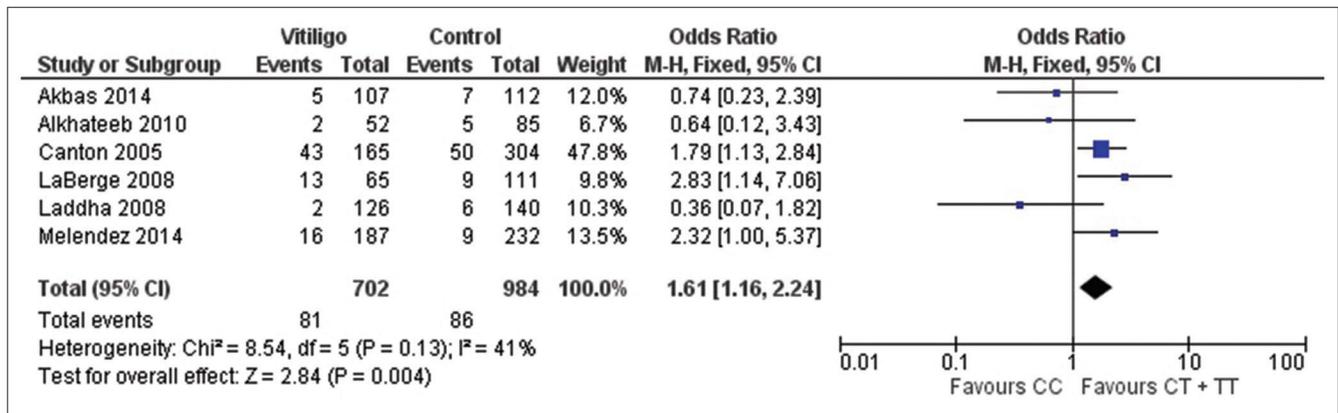
**Table 2: Summarized statistical result of meta-analysis**

Studies polymorphism	Number of studies	Sample size		Genetic model	Statistical model	OR (95% CI)	P <sub>z</sub>	I <sup>2</sup> (%)	P <sub>heterogeneity</sub>
		Case	Control						
PTPN+1858C→T	7	2094	3613	Allelic model	Fixed model	1.50 (1.32-1.71)	<0.001	35	0.16
				Dominant model	Fixed model	1.61 (1.16-2.24)	0.004	41	0.13
				Recessive model	Fixed model	4.82 (1.11-20.92)	0.04	0	0.96
				Homozygous model	Fixed model	5.34 (1.23-23.24)	0.03	0	0.95
				Codominant model	Fixed model	1.52 (1.09-2.13)	0.01	37	0.16

OR: Odds ratio, CI: Confidence interval



**Figure 2a:** Forest plots to assess the association between the protein tyrosine phosphatase, nonreceptor type 22 +1858C→T and vitiligo risk collectively in all the studies included in the meta-analysis. The squares and horizontal lines correspond to odds ratio and 95% confidence interval of specific study and the area of squares reflects study weightage (inverse of the variance). The diamond represents the pooled odds ratio and its 95% confidence interval. Meta-analysis under allelic model, showed association of protein tyrosine phosphatase, nonreceptor type 22 +1858C→T with vitiligo risk



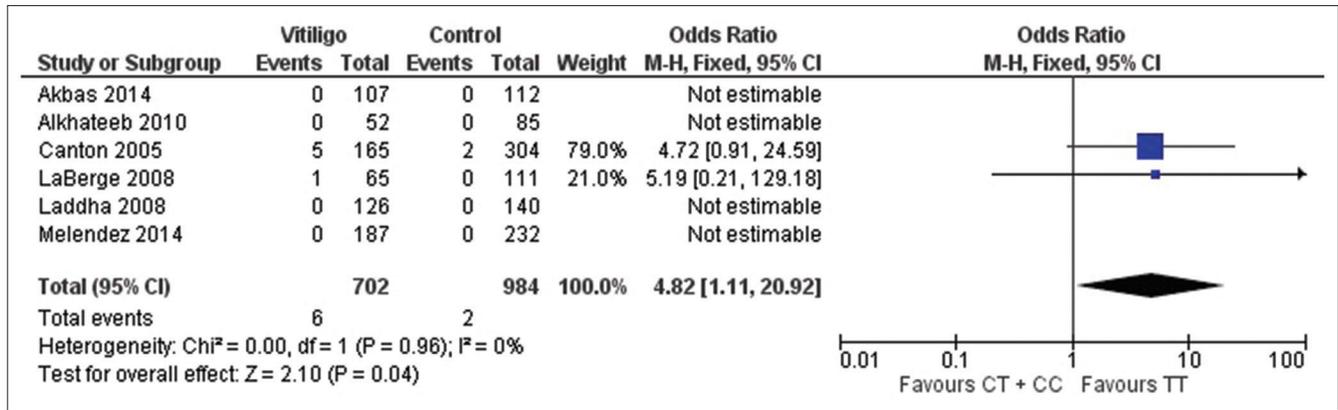
**Figure 2b:** Forest plots to assess the association between the protein tyrosine phosphatase, nonreceptor type 22 +1858C→T and vitiligo risk collectively in all the studies included in the meta-analysis. The squares and horizontal lines correspond to odds ratio and 95% confidence interval of specific study and the area of squares reflects study weightage (inverse of the variance). The diamond represents the pooled odds ratio and its 95% confidence interval. Meta-analysis under dominant model, showed association of protein tyrosine phosphatase, nonreceptor type 22 +1858C→T with vitiligo risk

P = 0.73); dominant (Begg’s P = 0.35, Egger’s P = 0.17); recessive (not estimable); codominant (Begg’s P = 0.35, Egger’s P = 0.19); homozygous (not estimable).

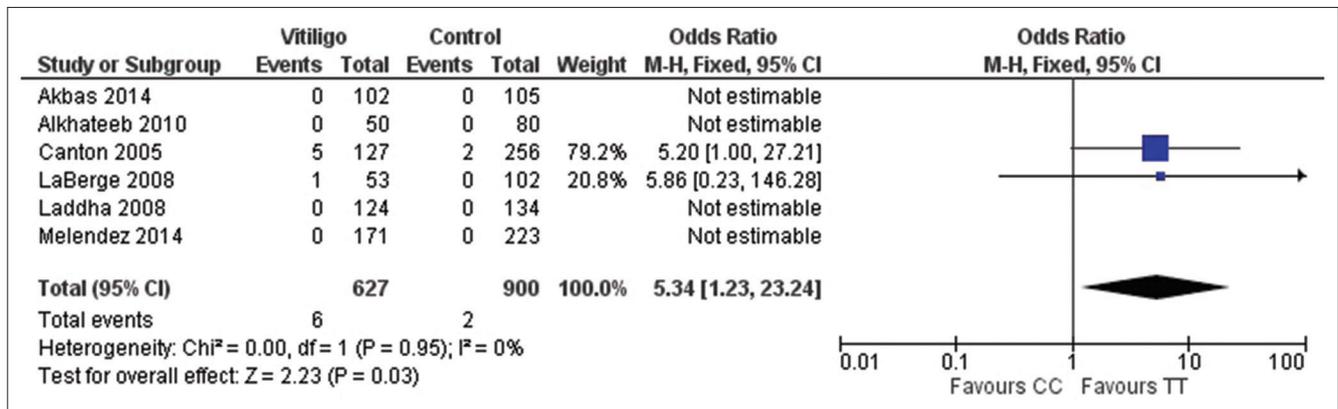
**Discussion**

Protein tyrosine phosphatase, nonreceptor type 22 gene encoding for lymphoid tyrosine phosphatase protein, forms a complex with C-terminal Src kinase protein, is known to play a key role in the regulation of T-cell activation and development by inhibiting

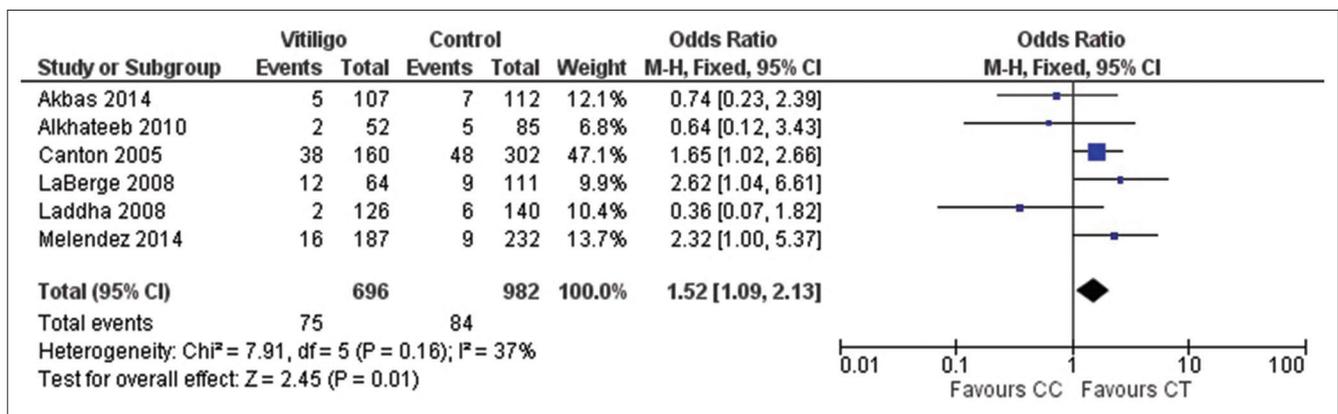
the T-cell receptor-signaling pathway and thus involved in the maintenance of central and peripheral tolerance in the body.<sup>14</sup> Protein tyrosine phosphatase, nonreceptor type 22 gene knockout experiments have demonstrated the elevated titers of T-cell-dependent antibodies, immunoglobulin G1 and immunoglobulin G2.<sup>7</sup> Variation in gene sequence such as +1858C→T variant has been found to be associated with overactivity of T-cell and may predispose an individual to autoimmune disease. Previous studies along with meta-analysis reports have shown that protein tyrosine phosphatase,



**Figure 2c:** Forest plots to assess the association between the protein tyrosine phosphatase, nonreceptor type 22 +1858C→T and vitiligo risk collectively in all the studies included in the meta-analysis. The squares and horizontal lines correspond to odds ratio and 95% confidence interval of specific study and the area of squares reflects study weightage (inverse of the variance). The diamond represents the pooled odds ratio and its 95% confidence interval. Meta-analysis under recessive model, showed association of protein tyrosine phosphatase, nonreceptor type 22 +1858C→T with vitiligo risk



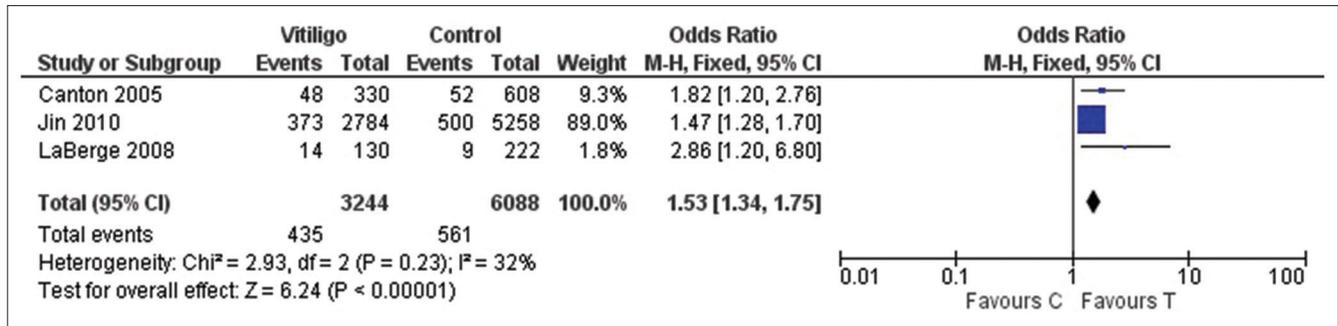
**Figure 2d:** Forest plots to assess the association between the protein tyrosine phosphatase, nonreceptor type 22 +1858C→T and vitiligo risk collectively in all the studies included in the meta-analysis. The squares and horizontal lines correspond to odds ratio and 95% confidence interval of specific study and the area of squares reflects study weightage (inverse of the variance). The diamond represents the pooled odds ratio and its 95% confidence interval. Meta-analysis under homozygous model, showed association of protein tyrosine phosphatase, nonreceptor type 22 +1858C→T with vitiligo risk



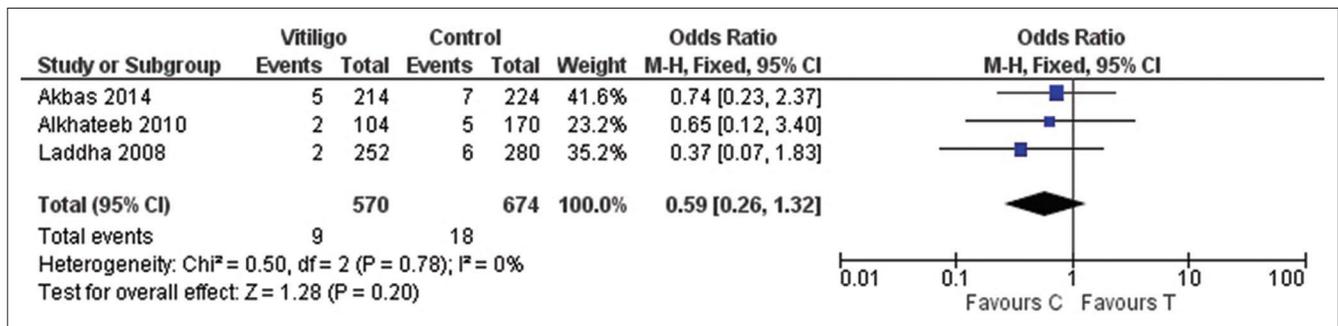
**Figure 2e:** Forest plots to assess the association between the protein tyrosine phosphatase, nonreceptor type 22 +1858C→T and vitiligo risk collectively in all the studies included in the meta-analysis. The squares and horizontal lines correspond to odds ratio and 95% confidence interval of specific study and the area of squares reflects study weightage (inverse of the variance). The diamond represents the pooled odds ratio and its 95% confidence interval. Meta-analysis under co-dominant model, showed association of protein tyrosine phosphatase, nonreceptor type 22 +1858C→T with vitiligo risk

nonreceptor type 22 +1858C→T has been associated with the number of autoimmune diseases.<sup>5,17,18,31,32</sup> The autoimmune nature of vitiligo has been supported by the presence of circulating melanocyte

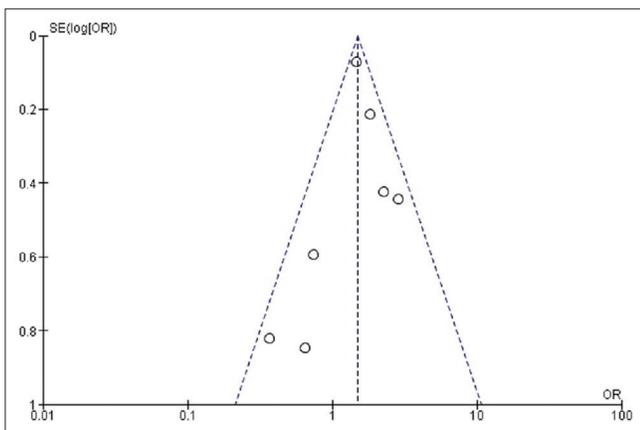
antibodies in human and animal models and its association with other autoimmune diseases. Based on this information, protein tyrosine phosphatase, nonreceptor type 22 polymorphism has been thought



**Figure 3a:** Forest plots to assess the association between the protein tyrosine phosphatase, nonreceptor type 22 +1858C→T and vitiligo risk according to the ethnicity, i.e., European, under allelic model



**Figure 3b:** Forest plots to assess the association between the protein tyrosine phosphatase, nonreceptor type 22 +1858C→T and vitiligo risk according to the ethnicity, i.e., Asian, under allelic model



**Figure 4:** Funnel plot to assess the publication bias. Odds ratio is plotted against the standard error of log odds ratio for studies on protein tyrosine phosphatase, nonreceptor type 22 +1858C→T polymorphism

to be associated with vitiligo pathogenesis. Several studies in the different ethnic background were conducted to assess the association of protein tyrosine phosphatase, nonreceptor type 22 +1858C→T with vitiligo susceptibility,<sup>8,22-27</sup> but inconsistent and inconclusive results were obtained. Studies by Cantón *et al.*, LaBerge *et al.* and Jin *et al.* reported association between the protein tyrosine phosphatase, nonreceptor type 22 +1858C→T polymorphism with vitiligo susceptibility among English, Romanian and English-North American population, respectively.<sup>23,25,26</sup> However, Laddha *et al.*, Alkhateeb *et al.* and Akbas *et al.* reported no association between the protein tyrosine phosphatase, nonreceptor type 22 +1858C→T polymorphism with vitiligo susceptibility among Indian, Jordanian and Turkish population, respectively.<sup>22,27,33</sup> Garcia-Melendez

*et al.* reported the association of protein tyrosine phosphatase, nonreceptor type 22 T allele with active vitiligo individual in the Mexican population.<sup>24</sup> Alkhateeb *et al.* suggested the association of the mutant variant with active vitiligo, but because of the limited number of patients, could not conclude their results.<sup>8</sup>

A total of nine studies were identified by systematic review of literature search, but two of the studies did not fulfill the inclusion criteria as mentioned in Figure 1. Meta-analysis of seven studies fulfilling inclusion criteria was performed to evaluate the association of protein tyrosine phosphatase, nonreceptor type 22 +1858C→T with vitiligo susceptibility with the aim of obtaining single conclusive result.<sup>8,22-27</sup> Our meta-analysis showed an overall significant association of protein tyrosine phosphatase, nonreceptor type 22 +1858C→T with vitiligo susceptibility under all genetic and allelic models suggesting that the protein tyrosine phosphatase, nonreceptor type 22 T allele is the risk factor in vitiligo pathogenesis. Results of this meta-analysis are inconsistent with the previous meta-analysis result conducted by Song *et al.*<sup>34</sup> In their study, only five available studies were included with the data obtained only from two ethnic populations, i.e., Asian and European. Two new case-control studies have been published after this meta-analysis.<sup>22,24</sup> Hence, to provide a comprehensive assessment of the association; we performed an updated meta-analysis of all available studies. Addition of these studies in our meta-analysis provided the advantage of (1) addition of new ethnic population, i.e., American in the meta-analysis which was lacking in the Song *et al.*,<sup>34</sup> (2) increase in the sample size resulting in more powerful statistical evidence and (3) reduction in the heterogeneity. Frequency of the risk allele (+1858T) varies in different populations and these associations could be related to these frequencies. Therefore, on stratifying data by ethnicity revealed that the protein tyrosine phosphatase, nonreceptor type 22 +1858C→T

polymorphism is associated with vitiligo susceptibility in European population only and not in Asian and American populations. The drawbacks of the present meta-analysis are (1) limited number of ethnic-based studies for protein tyrosine phosphatase, nonreceptor type 22 polymorphism, (2) small sample size and (3) data were not stratified by gender or vitiligo type because of insufficient information.

### Conclusion

In conclusion, meta-analysis results showed that the protein tyrosine phosphatase, nonreceptor type 22 +1858T-allele predisposes an European individual to vitiligo and thus uncovers the genetic factors involved in the pathogenesis of vitiligo. We suggest that greater number of ethnicity-based studies with more number of samples is required to further confirm this association.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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