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An in-depth analysis identifies two new independent signals in 11q23.3 associated with vitiligo in the Chinese Han population

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ABSTRACT

Background: Vitiligo is an autoimmune disease, characterized by progressive loss of skin pigmentation, which is caused by the interactions of multiple factors, such as heredity, immunity and environment. Recently, a single nucleotide polymorphism (SNP) rs638893 at 11q23.3 region was identified as a risk factor for vitiligo in genome-wide association studies and multiple SNPs in this region have been associated with other autoimmune diseases.

Objective: This study aims to identify additional susceptibility variants associated with vitiligo at 11q23.3 in the Chinese Han population.

Methods: We selected and genotyped 26 SNPs at 11q23.3 in an independent cohort including 2924 cases and 4048 controls using the Sequenom MassArray iPLEX® system. Bonferroni adjustment was used for multiple comparisons and *P* value $<1.92 \times 10^{-3}$ (0.05/26) was considered statistically significant.

Results: The A allele of rs613791 and G allele of rs523604 located in CXCR5 were observed to be significantly associated with vitiligo (OR = 1.21, 95% CI: 1.11–1.31, $P = 1.20 \times 10^{-5}$; OR = 1.14, 95% CI: 1.07–1.23, $P = 1.90 \times 10^{-4}$, respectively). The C allele of rs638893 (a previously reported one) located upstream of *DDX6* was also significantly associated with vitiligo (OR = 1.25, 95% CI: 1.12–1.38, $P = 3.04 \times 10^{-5}$). The genotypes distribution of 3 SNPs also showed significant differences between case and control (rs613791: $P = 7.00 \times 10^{-6}$, rs523604: $P = 4.00 \times 10^{-3}$, rs638893: $P = 1.20 \times 10^{-5}$, respectively). The two newly identified SNPs (rs613791 and rs523604) showed independent associations with vitiligo by linkage disequilibrium analysis and conditional logistic regression.

Conclusions: The study identified two new independent signals in the associated locus 11q23.3 for vitiligo. The presence of multiple independent variants emphasizes an important role of this region in disease susceptibility.

1. Introduction

Vitiligo is an autoimmune and acquired depigmentation disorder, characterized by progressive loss of skin pigmentation with plaque-like, multiple lesions of pigmentation incapacity, frequently hair and mucous membranes involvement [1,2]. Vitiligo is generally believed as a complex disorder with diverse prevalence across worldwide populations [3–6], and the interaction between multiple genetic and environmental factors can confer susceptibility of melanocyte destruction [1,7]. The pathogenesis of vitiligo, including genetic, immunological, neurohormonal, cytotoxic, oxidative stress and melanocyte loss, has been suggested [8]. Notably, several GWASs of vitiligo in Caucasian and Chinese Han population have identified thirty-eight susceptibility genes/loci (at genome-wide significance with $P < 5.0 \times 10^{-8}$) [9–14]. However, there might be other unknown susceptibility variants for this common disease.

The 11q23.3 region has provoked interest for its pleiotropic roles in several complex diseases. This 5.3Mb region contains multiple genes, including *PHLDB1*,*DDX6*, *TREH* and *CXCR5* [15]. Studies showed that SNPs at this region were associated with several diseases, for example, rs498872 for glioma [16], rs6421571 for primary biliary cirrhosis [17], rs630923 for multiple sclerosis [18], rs10892279 for celiac disease and rheumatoid arthritis [19]. A

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Table 1
Demographic details of the subjects.

	cases	control
Total samples	2924	4048
Average age (age)(SD)	26.89 ± 14.42	28.39 ± 10.36
Age arranged	1–77	1–85
Age of onset	21.89 ± 13.86	NA
Male	1489(50.92%)	1973(48.74%)
Female	1435(49.08%)	2075(51.26%)
Early onset/late onset	1624(57.49%)/1201(42.51%)	NA
Non segmental/segmental	2480(90.31%)/266(9.69%)	NA
With/without family history	366(13.38%)/2369(86.62%)	NA
With/without autoimmune diseases	91(3.11%)/2833(96.89%)	NA
Body surface involved(≤5%)/(>5%)	2417(85.65)/405(14.35%)	NA
With/without Koebner phenomenon	334(17.01%)/1629(82.99%)	NA

NA refers to not available.

recent association analysis of systemic lupus erythematosus (SLE) also identified three independent susceptibility variants in this region [15]. In the extended vitiligo GWAS, we identified rs638893 has a robust association with vitiligo ($P_{combined} = 2.47 \times 10^{-9}$, OR = 1.22) [13]. However, there are still many details remaining elusive for its high gene density.

It is possible that other genetic variants in this region are responsible for the consistent association with vitiligo. In this study, we performed a further analysis to examine the additional susceptibility variants for vitiligo in this region through deep replication.

2. Materials and methods

2.1. Study subjects

All samples were selected from the Han Chinese population through collaboration with multiple hospitals in China. In total, 1117 vitiligo patients and 1701 controls were selected from our vitiligo GWAS, while 2924 cases (1489 males and 1435 females with an average age of 26.88 years and arranging from 1 to 77 years) and 4048 controls (1973 males and 2075 females with an average age of 28.21 years and arranging from 1 to 85 years) were recruited for replication in this study (Table 1). The clinical diagnosis of all patients was confirmed by at least two experienced dermatologists. All controls were healthy individuals without vitiligo, any other autoimmune diseases or systemic disorders, and without any family history of vitiligo (including first-, second- and third-degree relatives). Clinical and demographic information was collected from both cases and controls with the same structured questionnaires used previously [11]. Case and control groups were matched for age, gender and ethnicity. All participants were provided written informed consent. This study was approved by the Institutional Ethical Committee of Anhui Medical University and was conducted according to Declaration of Helsinki principles.

Peripheral blood samples were collected from each subject. Genomic DNA was extracted from peripheral blood lymphocytes by standard procedures using FlexiGene® DNA kits (Qiagen,

Table 2
Comparison frequency of allele for 26 SNPs between vitiligo patients and controls.

SNP	Location	Allele[a]	Minor Allele Frequency		P value	OR(95%CI)	*P*-hwe	Call-rate
			Case	Control				
rs10892258	intergenic	A/G	0.22	0.23	2.70×10^{-1}	0.96(0.88–1.04)	9.64×10^{-1}	9.79×10^{-1}
rs654423	intron	T/C	0.24	0.23	3.10×10^{-1}	1.04(0.96–1.13)	9.64×10^{-1}	9.68×10^{-1}
rs613791	intron	A/G	0.22	0.19	$\mathbf{1.20 \times 10^{-5}}$	1.21(1.11–1.31)	8.77×10^{-1}	9.63×10^{-1}
rs566416	intron	G/T	0.11	0.11	8.80×10^{-1}	1.01(0.90–1.13)	8.66×10^{-1}	9.80×10^{-1}
rs12419235	intergenic	T/G	0.15	0.17	1.60×10^{-2}	0.89(0.81–0.98)	8.66×10^{-1}	9.80×10^{-1}
rs604096	intergenic	C/T	0.29	0.29	7.40×10^{-1}	0.99(0.92–1.06)	7.87×10^{-1}	9.75×10^{-1}
rs3922	utr variant	C/T	0.31	0.30	2.12×10^{-2}	1.09(1.01–1.18)	6.99×10^{-1}	9.60×10^{-1}
rs10892282	intron	C/G	0.26	0.28	6.65×10^{-2}	0.93(0.86–1.01)	6.62×10^{-1}	9.74×10^{-1}
rs497916	intron	T/C	0.23	0.22	1.00×10^{-1}	1.07(0.99–1.17)	6.62×10^{-1}	9.16×10^{-1}
rs10892306	intergenic	A/T	0.050	0.057	8.03×10^{-2}	0.87(0.75–1.02)	6.53×10^{-1}	9.69×10^{-1}
rs555356	intergenic	T/G	0.44	0.44	4.30×10^{-1}	0.97(0.91–1.04)	6.09×10^{-1}	9.89×10^{-1}
rs7929825	intron	G/C	0.20	0.18	4.32×10^{-3}	1.14(1.04–1.24)	5.44×10^{-1}	9.65×10^{-1}
rs3741331	utr variant	G/A	0.12	0.10	8.09×10^{-3}	1.16(1.04–1.29)	4.81×10^{-1}	9.73×10^{-1}
rs555649	intron	C/T	0.41	0.42	3.30×10^{-1}	0.97(0.90–1.04)	4.52×10^{-1}	9.72×10^{-1}
rs602716	intergenic	A/G	0.14	0.15	1.00×10^{-1}	0.92(0.84–1.02)	4.20×10^{-1}	9.80×10^{-1}
rs523604	intron	G/A	0.40	0.37	$\mathbf{1.90 \times 10^{-4}}$	1.14(1.07–1.23)	2.74×10^{-1}	9.72×10^{-1}
rs10892272	intergenic	G/C	0.16	0.16	6.10×10^{-1}	0.98(0.89–1.07)	2.11×10^{-1}	9.72×10^{-1}
rs4936444	intergenic	T/C	0.11	0.12	7.50×10^{-1}	0.98(0.88–1.09)	1.86×10^{-1}	9.68×10^{-1}
rs11216943	intergenic	A/G	0.22	0.22	7.30×10^{-1}	1.01(0.93–1.10)	1.51×10^{-1}	9.77×10^{-1}
rs663003	intergenic	A/G	0.32	0.32	7.80×10^{-1}	1.01(0.94–1.09)	1.19×10^{-1}	9.62×10^{-1}
rs7115634	intron	G/A	0.48	0.47	4.40×10^{-1}	1.03(0.96–1.10)	1.18×10^{-1}	9.07×10^{-1}
rs638893	upstream	C/T	0.14	0.11	$\mathbf{3.04 \times 10^{-5}}$	1.25(1.12–1.38)	6.30×10^{-2}	9.52×10^{-1}
rs4938576	intergenic	G/T	0.44	0.45	4.50×10^{-1}	0.97(0.91–1.04)	4.60×10^{-2}	9.42×10^{-1}
rs573905	intron	A/G	0.50	0.21	4.55×10^{-2}	3.87(0.94–15.98)	2.70×10^{-2}	1.90×10^{-2}
rs10892301	intergenic	A/G	0.46	0.45	2.70×10^{-1}	1.04(0.97–1.12)	2.20×10^{-2}	9.43×10^{-1}
rs587263	intergenic	A/G	0.46	0.48	4.32×10^{-2}	0.93(0.86–1.00)	6.00×10^{-3}	8.25×10^{-1}

P value < 0.0019 (0.05/26) were considered to be statistically significant (with Boniferroni corrections).
[a] Minor allele/major allele; P values of less than 0.05/26 were considered to be statistically significant (with Bonferroni corrections).