

The analysis of genetics and associated autoimmune diseases in Chinese vitiligo patients

Zheng Zhang · Sheng-Xin Xu · Feng-Yu Zhang · Xian-Yong Yin ·
Sen Yang · Feng-Li Xiao · Wen-Hui Du · Jian-Feng Wang ·
Yong-Mei Lv · Hua-Yang Tang · Xue-Jun Zhang

Received: 26 March 2008 / Revised: 13 July 2008 / Accepted: 2 September 2008
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Abstract Vitiligo is a common skin and hair depigmentary disorder that results from selective destruction of melanocytes. It occurs in a typical multifactorial, polygenic inheritance. Several studies have indicated that vitiligo is associated with some autoimmune diseases. In this paper we examined 6,516 vitiligo patients including clinical characteristics, familial involvement, and their association with other autoimmune diseases. Compared with sporadic vitiligo probands, familial vitiligo probands have earlier age onset and longer disease duration. The prevalences of four autoimmune diseases namely rheumatoid arthritis, chronic urticaria, alopecia areata and psoriasis, were significantly elevated in generalized vitiligo probands and their first-degree relatives. The prevalences of chronic urticaria, rheumatoid arthritis, psoriasis were much higher in familial generalized vitiligo probands. In addition, the prevalences of diabetes mellitus and asthma

were also higher in familial vitiligo probands. These findings indicate that generalized vitiligo may share common genetic aetiologic links with other autoimmune diseases, and the genetic component of familial generalized vitiligo is stronger.

Keywords Vitiligo · Autoimmunity · Rheumatoid arthritis · Chronic urticaria · Alopecia areata · Psoriasis

Introduction

Vitiligo is one of the most common depigmentary disorders of the skin and hair that results from selective destruction of melanocytes. The prevalence of vitiligo in China is approximately 0.19% [37]. Most cases occur sporadically, about 10–38% [12, 22, 25, 34] patients have family history and its inheritance pattern is consistent with a polygenic trait. In recent years, increasing attention has been paid to examine the genetic factors of vitiligo, and more than 4 loci have been found to be susceptible to vitiligo [2, 4, 5, 10, 19, 24, 38].

It is also believed that vitiligo has an autoimmune basis [26]. And vitiligo itself is a component of the APECED (APS1) and Schmidt (APS2) multiple autoimmunity syndromes [29]. A number of studies have suggested the association of vitiligo with other autoimmune diseases, including thyroid disease [18, 30] pernicious anemia [3, 7, 11], diabetes mellitus [8] alopecia areata [32], and Addison's disease [9, 23].

Our group had previously described clinical profiles of vitiligo in 3,742 Chinese patients, and found that patients with vitiligo were more likely to be affected with rheumatoid arthritis, ichthyosis, chronic urticaria, and alopecia

This work was funded by the grants from National Natural Science Foundation of China (200530530670).

Z. Zhang · S.-X. Xu · F.-Y. Zhang · X.-Y. Yin · S. Yang ·
F.-L. Xiao · W.-H. Du · J.-F. Wang · Y.-M. Lv ·
H.-Y. Tang · X.-J. Zhang (✉)
Institute of Dermatology and Department of Dermatology,
The First Affiliated Hospital, Anhui Medical University,
81 Meishan Road, 230032 Hefei, Anhui,
People's Republic of China
e-mail: ayxj@vip.sina.com; ayxj@mail.hf.ah.cn

Z. Zhang · S.-X. Xu · F.-Y. Zhang · X.-Y. Yin · S. Yang ·
F.-L. Xiao · W.-H. Du · J.-F. Wang · Y.-M. Lv ·
H.-Y. Tang · X.-J. Zhang
The Key Laboratory of Gene Resource Utilization for Severe
Genetic Diseases, Ministry of Education and Anhui Province,
Hefei, China

areata [20]. To further understand the genetic component of vitiligo and vitiligo-associated autoimmune diseases, we conducted this study in an independent group of vitiligo patients. In this paper we present an analysis of genetic characteristic and associated autoimmune diseases of 6,516 vitiligo patients. Probands' first-degree relatives were also investigated, and the difference in prevalence of autoimmune disease was compared between familial vitiligo probands and sporadic patients.

Materials and methods

Study population

All patients in this study were outpatients who were recruited to our collaborative network established for genetic study of skin diseases across China. The network study team consisted of dermatologists from hospitals located in four cities: Hefei, Xiangfan, Xi'an, and Beijing, which represents southeast, northwest and north geographic regions in China. Totally, 6,516 patients (probands) diagnosed with vitiligo were selected from December 2003 to August 2007. Altogether, 6,199 patients were analyzed, including 3,276 (52.8%) male probands and 2,923 (47.2%) female probands with mean ($\pm$ SD) ages of 24.5 ($\pm$ 14.6) years. The median ($\pm$ Q) disease duration was 18 ($\pm$ 54) months.

Diagnostic criteria

All the patients were diagnosed as vitiligo by two independent dermatologists. Clinical types of vitiligo in this study were subclassified as focal (≥ 1 macule in one area, but not clearly in a segmental or zosteriform distribution), vulgaris (scattered macules), universal (complete or nearly complete depigmentation over the body), acrofacial (distal parts of the extremities and face), and segmental (≥ 1 macule involving a unilateral segment of the body) [15]. Focal, universal, acrofacial, and vulgaris are subtypes of generalized vitiligo. Patients with piebaldism and other monogenic hypomelanoses, including tuberous sclerosis, post-inflammatory/lymphoma-associated hypopigmentation (e.g., in psoriasis, atopic dermatitis, and mycosis fungoides), post-inflammatory/infectious hypopigmentation (e.g., in pityriasis versicolor and leprosy), post-traumatic leucoderma, melanoma-associated leucoderma, melasma, and drug-induced depigmentation were excluded. Patients' first degree relatives include siblings and children. Patients' second degree relatives include grandparents, uncle, aunt, nephew, niece, and half-sibling. Patients' third degree relatives include great grandparent, great aunt, great uncle, and first cousin.

Data collection

Patient information was collected through face to face interview conducted by dermatologists using standard instrument. Information includes patient's demographics, age of onset, current age and gender of each first-degree relative. Family structure and self-reported autoimmune disorders were collected in both the proband and their relatives. To reduce the possible recall bias, another member of each proband's family was requested to confirm the information about family history. All patients including probands and their relatives were given a diagnosis by a dermatologist. Due to missing data, 317 out of 6,516 patients (4.86%) were excluded in the final analysis. This study was approved by the Medical Ethics Committee of Anhui Medical University.

Statistical analysis

Data were analyzed using Chi-square test, Student's *t* test and Rank test. For qualitative data, Chi-square was used to compare the differences in prevalence between sporadic probands and familial ones. *T* test was used to compare the mean of quantitatively measured data between sporadic and familial probands. When the data did not fit normal distribution, rank test was used. The level of $P < 0.01$ was used as statistical significance.

Results

Proband characteristics

A total of 6,516 patients were enrolled in the study, and 6,199 patients completed questionnaire and without missing values were used for the questionnaire analysis. Table 1 shows the distribution and demographics of vitiligo probands, 52.8% of the patients were males and 47.2% were females. Proband ages ranged from 1 to 91 year (mean 24.5 ± 14.6). The age of disease onset ranged from birth to 91 years (mean 20.1 ± 13.7 years). Disease duration ranged from 0 to 961 months (median 18 months).

There were 1,027 multiple familial vitiligo probands and 5,172 sporadic ones. The mean age onset of familial vitiligo probands was earlier than sporadic ones (18.7 ± 12.5 vs. 20.4 ± 13.9 years, $P < 0.01$). The median disease duration of familial vitiligo probands was longer than sporadic probands (24 vs. 16 months $P < 0.01$).

Most vitiligo probands had generalized 5,601 (90.4%) form of the disease. As shown in Table 2, of the 5,601 patients with generalized vitiligo, 1,654 (26.7%) had the focal subtype, 2,981 (48.1%) had universal subtype, 197 (3.2%) had universal subtype and 769 (12.4%) had the

Table 1 Distribution of demographics of familial and sporadic proband

	Total	Sporadic probands	Familial vitiligo probands	Significance
Age				
Mean	24.5 ± 14.6	24.5 ± 14.7	24.5 ± 14.3	Ns
Range	1–91	1–82	1–91	
Gender				
Male (%)	3276(52.8)	2753(53.2)	523(50.9)	<i>P</i> = 0.19
Female (%)	2923(47.2)	2419(46.8)	504(49.1)	
Age of onset				
Mean (±SD)	20.1(± 13.7)	20.4 ± 13.9	18.7 ± 12.5	<i>P</i> < 0.01
Range	0–91	0–91	0–70	
Disease duration				
Median (±Q)	18 ± 54	16 ± 48	24 ± 76	<i>P</i> < 0.01
Range	0–961	0–961	0–601	

Ns no statistically significant different

Table 2 Clinical features of vitiligo probands

Feature	Patients(%)
Forms of disease	
Focal	1,654(26.7)
Vulgaris	2,981(48.1)
Universal	197(3.2)
Acrofacial	769(12.4)
Segmental	598(9.6)
Disease activity	
Active	4,215(68)
Stable	1,984(32)
% of body surface involvement	
<5%	4,850(78.3)
5–20%	866(14.0)
>20%	483(7.8)

acrofacial subtype. Only 9.6% probands had segmental vitiligo. Most probands had active (68%) forms of vitiligo. Extent of disease was scored by degree of skin surface involvement which was divided into three levels: severe (>20%), moderate (5–20%), and mild (<5%). The majority of probands had <5% of skin surface involved. 14.0% had 5–20% involved skin surface and 7.8% had >20% involved skin surface.

Associated autoimmune diseases

Diseases associated with generalized as well as segmental vitiligo are summarized in Table 3. Most autoimmune diseases associated with generalized vitiligo. Only 6 of 598 segmental vitiligo probands had autoimmune diseases. Table 4 provides the prevalences of autoimmune diseases associated with generalized vitiligo. It was shown that the prevalences of rheumatoid arthritis, chronic urticaria,

Table 3 Vitiligo associated diseases

Associated diseases	Type of vitiligo		Total
	Generalized	Segmental	
Inflammatory bowel disease	0	0	0
Hyperthyroidism	71	1	72
Hypothyroidism	61	1	62
Diabetes mellitus	39	1	40
Rheumatoid arthritis	123	1	124
Asthma	23	2	25
Chronic urticaria	48	0	48
Alopecia areata	50	0	50
Psoriasis	19	0	19
Systemic lupus erythematosus	0	0	0
Dermatomyositis	0	0	0
Myasthenia gravis	1	0	1
Total	435	6	441

alopecia areata and psoriasis were elevated in both generalized vitiligo probands and their relatives. Among the 5,601 generalized vitiligo probands, one of the most common immune-mediated disease was rheumatoid arthritis which affected 2.20% of patients (123), 6.5 times increased (*P* < 0.01) from the reported 0.34% in general population. Among the 18,705 first degree relatives of generalized vitiligo probands, 0.59% (110) of them were reported as having clinical rheumatoid arthritis, more than twice high as that in general population prevalence (*P* < 0.01). The prevalence of alopecia areata was also significantly elevated in generalized vitiligo probands and their relatives. Among 5,601 generalized vitiligo probands, 0.89% (50) had had alopecia areata, a tenfold increase (*P* < 0.01) compared with the population prevalence of 0.085% (Table 4). Similarly, 0.13% (25) of generalized vitiligo probands' first-degree relatives were reported to have had alopecia areata

Table 4 Associated autoimmune disorders in vitiligo probands and their first-degree relatives

Disease	Probands (<i>n</i> and %)			First-degree relatives (<i>n</i> and %)			Population prevalence (%)		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
	<i>n</i> = 5,601	<i>n</i> = 3,162	<i>n</i> = 2,439	<i>n</i> = 18,705	<i>n</i> = 9,256	<i>n</i> = 9,449			
Inflammatory bowel disease	0	0	0	ND	ND	ND	0.13–0.16 × 10 ³ ^a		
Hyperthyroidism	71 1.27	20 (0.63)*	51 2.09	72 0.38	16 0.17	56 0.59	1.194 ^b	0.468 ^b	1.917 ^b
Hypothyroidism	61 1.10	18 (0.57)*	43 1.76	70 0.37	15 0.16	55 0.58	1.034 ^b	0.419 ^b	1.647 ^b
Diabetes mellitus	39 0.70	24 (0.76)*	15 0.62	16 0.09	9 0.10	7 0.07	0.674 ^b	0.684 ^b	0.662 ^b
Rheumatoid arthritis	123 (2.20)*			110 (0.59)*			0.32–0.34 ^c		
Asthma	23 0.41			30 0.16			0.41 ^b		
Chronic urticaria	48 (0.86)*			116 (0.62)*			0.1 ^b		
Alopecia areata	50 (0.89)*	38 (1.20)*	12 (0.49)*	25 (0.13)*	17 (0.18)*	8 0.08	0.085 ^b	0.133 ^b	0.035 ^b
Psoriasis	19 (0.34)*			44 (0.24)*			0.123 ^b		
Systemic lupus erythematosus	0			3 0.02			0.03 ^b		
Dermatomyositis	0			0			0.5–8 × 10 ³ ^d		
Myasthenia gravis	1 (0.02)	1 (0.02)		0			0.05 ^e		

ND not done

* $P < 0.01$ ^a Data derived from [40], ^bData derived from [20], ^cData derived from [39], ^dData derived from [35], ^eData derived from [36]

($P < 0.01$); Alopecia areata was more prevalent in males (1.20%) than in females (0.49%). The prevalence of psoriasis was 0.34% (19) among generalized vitiligo probands, notably higher than that in both general population (0.12% $P < 0.01$), and generalized vitiligo probands' first degree relatives (0.24% $P < 0.01$). The prevalence of chronic urticaria was 0.86% (48) among generalized vitiligo probands, elevated for about eight times compared with the population prevalence of 0.1% ($P < 0.01$), 0.62% (116) among probands' first degree relatives.

No significant increase in the prevalence of hypothyroidism, hyperthyroidism, diabetes mellitus, SLE, asthma, and dermatomyositis was observed.

Associated autoimmune disorders in familial vitiligo probands

Of 978 familial generalized vitiligo probands, 11% (112) have at least one additional autoimmune disease. As

shown in Table 5, the prevalence of chronic urticaria was 1.6% (16) in the familial generalized vitiligo probands, significantly more than 0.9% (48) prevalence among generalized vitiligo probands. The prevalence of psoriasis in familial generalized vitiligo probands was 0.8% (9), also more than its 0.3% (19) prevalence among total generalized vitiligo probands. Rheumatoid arthritis was reported in 21% (21) of the familial generalized vitiligo probands, similar to that among total generalized vitiligo probands.

As of several other autoimmune diseases, we did not find increased prevalence among generalized vitiligo probands occurred at elevated prevalence among the familial generalized vitiligo probands. Diabetes mellitus occurred in 3.3% (32) of the familial vitiligo probands, significantly more than its population prevalence 0.674% ($P < 0.01$). Asthma also occurred in 0.8% (8) of the familial vitiligo probands, more than its prevalence of 0.41% in general population.

Table 5 Associated autoimmune disorders in familial generalized vitiligo probands

Disease	Probands (<i>n</i> = 978)	Population prevalence (%)
Inflammatory bowel disease	0	1.38×10^3
Hyperthyroidism	14(1.5%)	1.194
Hypothyroidism	12(1.2%)	1.034
Diabetes mellitus	32(3.3%)*	0.674
Rheumatoid arthritis	21(2.1%)*	0.32–0.34
Asthma	8(0.8%)*	0.41
Chronic urticaria	16(1.6%)*	0.1
Alopecia areata	0	0.085
Psoriasis	9(0.8%)*	0.123
Systemic lupus erythematosus	0	0.03
Dermatomyositis	0	$0.5\text{--}8 \times 10^3$
Myasthenia gravis	0	0.05
Total	112(11.5%)	

* $P < 0.01$

Discussion

The clinical characteristics of vitiligo in Chinese study are generally similar to those reported elsewhere [14, 16]. The most frequent pattern was generalized vitiligo involving less than 5% of the skin surface. Most people had active form of vitiligo.

Previous studies have shown that the pathogenesis of vitiligo is related to immunity and heredity [28, 31], but there were still limited epidemiologic data in Chinese vitiligo patients, and little is known about its association with autoimmune disease. It is interesting to have a better understanding of the genetic component in both vitiligo and vitiligo-associated autoimmune disease.

The strongest evidence for genetic factors in the pathogenesis of vitiligo comes from studies of patients' close relatives. A positive family history incidence ranged from 10 to 38% [12, 22, 25, 34]. As we have pointed out previously [20], relative risks for first- and second-degree relatives of probands were significantly elevated compared with general population; but not for third-degree relatives. The mean age onset of vitiligo was slightly higher in familial vitiligo probands than the sporadics'. And the disease duration of familial vitiligo probands is much longer. These observations of earlier age of disease onset, longer disease duration in familial cases and decreased disease risk with increasing genetic distance from an affected proband, are classic characteristics of a polygenic trait.

Different pathogenic mechanisms could account for the various clinical types of vitiligo: the neural theory is usually related to segmental vitiligo, whereas the autoimmune

hypothesis is thought to be involved in the generalized form of the disorder. Several CTLA-4 polymorphic alleles are associated with vitiligo, however, that significant associations of vitiligo with CTLA-4 polymorphic markers is only seen in patients with concomitant autoimmune disease. This raises the possibility that there are two forms of vitiligo where only a subgroup of patients has the disease as a result of melanocyte autoimmune destruction [28]. Here we analyzed generalized vitiligo probands and segmental vitiligo probands separately. We found that most autoimmune diseases associated with generalized vitiligo (7.8%), only four autoimmune diseases associated with segmental vitiligo (0.7%).

The prevalences of four autoimmune diseases, namely rheumatoid arthritis, chronic urticaria, alopecia areata and psoriasis were significantly elevated in generalized vitiligo probands and their first-degree relatives. The prevalences of these vitiligo associated autoimmune diseases were likewise all increased in probands' first-degree relatives. These findings suggested that vitiligo and these associated autoimmune diseases may share common aetiological factors, and common factors mediating susceptibility to this constellation of diseases include genetics. One of the most common reported vitiligo associated autoimmune disease is thyroid dysfunction. But the prevalence of thyroid disease in our study is equal to the prevalence among general population. The prevalence, whether the same or different from the normal population, suggests that the association is not strongly related to vitiligo in a simple way.

Alkhateeb et al. [1] reported that more than 20% of the generalized vitiligo patients had at least one autoimmune disease. We found that only 7.77% of vitiligo probands had autoimmune disease in our population. Recent retrospective studies of large vitiligo patient series in India [13] and Nigeria [27] have generally agreed with our findings in China, and these findings all reported lower associated autoimmune diseases than Alkhateeb's report, especially thyroid disease. These could be due to several reasons. Firstly, in our study the mean age of the patient group was 24.5, lower than 34–42 years reported by Alkhateeb et al. Thus, most of the patients here were under the peak ages onset of associated diseases. Secondly the prevalences of some autoimmune diseases were lower in China. For example the prevalence of inflammatory bowel disease in Chinese is 1.38×10^5 [40], much lower than that in Caucasians (0.37%) [21]. Thirdly genetic factor also affected the prevalence of associated autoimmune disease. In Caucasians, significant vitiligo linkage signals have been detected on chromosomes 7 (AIS2), 8 (AIS3), and 17p [10, 33]. The chromosome 7 and 17p linkage signals appear to derive primarily from families segregating to the vitiligo and other vitiligo-associated autoimmune diseases. In China genetic linkage studies have detected an entirely different set of

linkage signals in familial generalized vitiligo [6], particularly on chromosome 4q13–q21, but also including signals at 1p36, 6p21–22, 6q24–25, 14q12–q13, and 22q12, none of which align with the linkage signals observed in Caucasian families, thus suggesting that different genes may be involved in the pathogenesis of vitiligo and associated autoimmune disease in different populations around the world. Finally, environmental factor also affect the prevalence of associated autoimmune disease. For example, a high dietary intake of vitamin B12 by the Chinese may prevent the occurrence of pernicious anaemia [17].

In the 978 familial vitiligo probands studied here, 12% reported at least one another autoimmune disease except vitiligo. Among the probands the prevalences of rheumatoid arthritis, chronic urticaria and psoriasis were again elevated. We also observed significantly elevated prevalences of diabetes mellitus and asthma in familial probands, which had not been significantly elevated among total probands. These findings provide strong support for a greater genetic component of risk for both vitiligo and specific vitiligo-associated autoimmune diseases in familial vitiligo than in sporadic ones.

Overall, our findings provided strong support for an autoimmune aetiology of vitiligo including both genetic and non-genetic components. In familial vitiligo probands the genetic component is stronger. The finding of association between vitiligo and other autoimmune diseases, may yield new insights into the pathogenesis of these diseases, and shed more light on improvement in both treatment and prevention of these disorders.

Acknowledgments This work was funded by the grants from National Natural Science Foundation of China (200530530670). We thank all the individuals who have so willingly participated in this study. And we thank Yanfeng Zou for his help in statistic analysis of this study.

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