Genetic epidemiology and heritability of vitiligo in the Qassim region of Saudi Arabia

A. Alzolibani

ABSTRACT

Aim: Assessment of consanguinity and inheritance patterns in relation to clinical subtypes of vitiligo among Saudi cases in the Qassim region based on a vitiligo case series during 2008 taken from the Qassim University–affiliated referral center.

Methods: This study included 111 randomly selected Saudi probands affected by vitiligo and their families. They included 61 males and 50 females. Their mean age of onset was 19.13 ± 11.97 years. Data were collected using a questionnaire administered by professional dermatologists emphasizing the clinical features as well as consanguinity and segregation pattern. Genetic analyses for inbreeding coefficient, mode of inheritance, and heritability were statistically analyzed.

Results: Out of 111 probands, the frequencies of focal, vulgaris, universal, and acrofacial subtypes were 32.4%, 31.5%, 9.9%, and 26.1%, respectively. Parental consanguinity was positive in 32.4% of cases and first-cousin consanguinity in 22.5% with an inbreeding coefficient of 0.015. The family history was positive in 56.8% of cases. The mean age of onset was 19.13 ± 11.97 years with a median of 17 years. The median age of onset was lower for consanguineous cases and cases with a positive family history. Inheritance patterns coincided more with the multifactorial model, especially for the vulgaris subtype followed by the acrofacial subtype, and coincided least with the focal subtype. Heritability or the genetic contribution to the disease showed a high weighted mean of 0.54.

Conclusion: Genetic factors contribute to the evolution of vitiligo among Saudi families. Discouraging consanguineous marriage is a potential prevention measure. Genetic factors contribute to the evolution of vitiligo among tribal areas of the Saudi community probably through the high consanguinity rate. In that respect, family counseling can be attempted that would discourage consanguinity and combat probable interactive environmental and health factors.

KEY WORDS

Saudi Arabia, vitiligo, genetics

Introduction

Vitiligo is a hypopigmentation disorder affecting 1 to 4% of the world population. Fifty percent of cases appear before the age of 20 years, and the disfigurement results in psychiatric morbidity in 16 to 35% of those affected (1).

Familial aggregation of vitiligo was noted as early as 1933 (2), suggesting that genetic factors might have an important effect on the development of vitiligo (3, 4). Although vitiligo aggregates in families, it does not appear to segregate in a simple mendelian pattern (5–8). Previously, an autosomal recessive model of vitiligo that took the variability of the age of onset into account was proposed, suggesting that there might be genes at three or four autosomal loci controlling vitiligo (9, 10). This was supported by the high frequency of vitiligo and other autoimmune diseases in isolated inbred communities. On the other hand, the actual onset of vitiligo in genetically susceptible individuals seems to require exposure to environmental triggers (11, 12).

Attempts to identify genes involved in vitiligo susceptibility have involved gene expression studies, allelic association studies of candidate genes, and genome-wide linkage analyses to discover new genes. These studies have begun to shed light on the mechanisms of vitiligo pathogenesis. It is anticipated that discovery of biological pathways of vitiligo pathogenesis will provide novel therapeutic and prophylactic targets for future approaches to the treatment and prevention of vitiligo and its associated autoimmune diseases (13).

This study addresses the genetic background of vitiligo in Saudi subjects from the Qassim region. This area has some interesting demographic characteristics in terms of being a tribal area with many consanguineous marriages and family aggregation of diseases.

Subjects and methods

This study comprised 111 unrelated Saudi probands affected with vitiligo and their families up to third-degree relatives. These cases were selected randomly from patients attending the Dermatology Outpatient Clinics, Qassim University, Saudi Arabia during 2008. After signing informed consents, the probands were interviewed by professional dermatologists to confirm the diagnosis of vitiligo and fill out a relevant questionnaire. Items included in the questionnaire were: name, address, telephone number, current age, sex, clinical classification, age of onset, and course of the disease, in addition to current age and sex of each first-degree relative, numbers of second- and third-degree relatives, and numbers of people affected by vitiligo among all relatives. Clinical subtypes of vitiligo in this study were subclassified as focal (≤ 2% depigmentation, one or more macules in one area, but not clearly in a segmental or zosteriform distribution), vulgaris (> 2% depigmentation, scattered macules), universal (complete or nearly complete depigmentation over the body), and acrofacial (distal parts of the extremities and face) (14). Mucosal vitiligo and hair involvement were also emphasized. This study was approved by the Scientific and Ethical Committees of Qassim University, Saudi Arabia.

Statistical methods

Consanguinity analysis and inbreeding coefficients were calculated according to the formula given by Fraser and Mayo (15). The observed relative frequency (s/q) was estimated by dividing frequency in sibs (s) by frequency in the general population (q). Segregation analysis was done by comparing the observed sib frequency (s/q) to the expected frequency for various modes of inheritance. Heritability (h') and its standard error (SE, h2) were deducted from frequency of vitiligo in the general population (g) and in relatives of affected individuals (16, 17).

Results

One hundred and eleven probands comprising 61 males and 50 females were included in this study. Their mean age was 26 ± 12.6 years with a median of 24 years. The mean duration of the disease was 6.89 years. The frequency of focal, vulgaris, universal, and acrofacial subtypes was 36 (32.4%), 35 (31.5%), 11 (9.9%), and 29 (26.1%), respectively. Interestingly, no single case of segmental subtype was encountered throughout this study. A positive family history of vitiligo was obtained in 63 (56.8%) cases. Parental consanguinity was present in 36 (32.4%) cases. Particularly high first cousin consanguinity (22.5%) resulted in a relatively high coefficient of inbreeding of 0.015 (Table 1). The mean age of onset in our patients was 19.13 ± 11.97 years with a median of 17 years. The median age of onset was lower for consanguineous cases and cases with a positive family history (12.6 years and 13.0 years, respectively).

The analysis of the different consanguinity patterns among the cases studied related to

Table 1. Consanguinity pattern and coefficient of inbreeding in vitiligo cases.

Parameter	Total	First cousin	First cousin once removed	Second cousin	Third cousin
n (*N* = 111)	36	25	2	1	8
%	32.4%	22.5%	1.8%	0.9%	7.2%
F	0.015	0.014	0.00056	0.00014	0.0003

F = inbreeding coefficient

Table 2. Consanguinity pattern related to clinical subtype.

Parameter	Negative	First cousin	Others	χ^2 (π)
Clinical subtypes				
Focal	27 (75.0%)	6 (16.7%)	3 (8.3%)	0.27
Vulgaris	25 (71.4%)	8 (22.9%)	2 (5.7%)	
Universal	4 (36.4%)	4 (36.4%)	3 (27.3%)	
Acrofacial	19 (65.5%)	7 (24.1%)	3 (10.3%)	
Mucosal involvement				
Positive	14 (73.7%)	2 (10.5%)	3 (15.8%)	303
Negative	61 (66.3%)	23 (25.0%)	8 (8.7%)	
White hair				
Positive	7 (58.3%)	2 (16.7%)	3 (25.0%)	0.177
Negative	68 (68.7%)	23 (23.2%)	8 (8.1%)	
Skin type				
Type III	13 (100.0%)	0 (0.0%)	0 (0.0%)	0.029
Type IV	62 (63.3%)	25 (25.5%)	11 (11.2%)	
Duration				
≤ 5 years	44 (72.1%)	13 (21.3%)	4 (6.6%)	0.36
> 5 years	31 (62.0%)	12 (24.0%)	7 (14.0%)	

different disease subtypes and clinical presentations is shown in Table 2. Parental consanguinity was highest among universal cases (63.6%), followed by acrofacial (34.5%), vulgaris (28.6%), and focal (25.0%) case-subtypes; however, the difference was non-significant. A high, but statistically non-significant, consanguinity rate was also associated with mucosal and hair involvement, and longer duration of the disease. Consanguinity was significantly higher among cases with skin type IV as compared to those with other types ($p = 0.008$).

A positive family history was noted to be significantly high among cases with the vulgaris subtype (80.0%), followed by acrofacial (69.0%), universal (45.5%), and focal subtypes (27.8%). A significantly high rate of family history was associated with skin type IV ($p = 0.044$). A positive family history of the disease was also associated with longer duration of the disease but the difference was non-significant (Table 3).

The inheritance pattern obtained using the frequency of vitiligo among sibs in relation to the general population coincided more with the multifactorial model especially for the vulgaris subtype, followed by the acrofacial, universal, and focal subtypes (Table 4).

Within the 111 families, 55 of the first-degree relatives (1,196), 41 of the second-degree relatives (1,985), and 46 of the third-degree relatives (5,848) of probands were also affected with vitiligo (5.00%, 2.07%, and 0.79%, respectively). Frequency among sibs was highest in the vulgaris subtype (8.0%), followed by 6.8% in the acrofacial subtype, 5.9% in the universal subtype, and only 0.8% in the focal subtype. Calculation of the heritability (the genetic contribution to the disease) showed a high weighted mean of 54.0% (Table 5).

Table 3. Family history related to clinical subtype, mucosal and hair involvement, and disease severity.

Parameter	Family history		p
	Positive	Negative	
Clinical subtypes			
Focal (36)	10 (27.8%)	26 (72.2%)	.000**
Vulgaris (35)	28 (80.0%)	7 (20.0%)	
Universal (11)	5 (45.5%)	6 (54.5%)	
Acrofacial (29)	20 (69.0%)	9 (31.0%)	
Mucosal involvement			
Positive (19)	14 (73.7%)	5 (26.3%)	.102
Negative (92)	49 (53.3%)	43 (46.7%)	
White hair			
Positive (12)	7 (58.3%)	5 (41.7%)	.907
Negative (99)	56 (56.6%)	43 (43.4%)	
Clinical severity			
Type III (13)	4 (30.8%)	9 (69.2%)	.044*
Type IV (98)	59 (60.2%)	39 (39.8%)	
Duration			
≤ 5 years	34(55.7%)	27(44.3%)	0.81
> 5 years	29(58.0%)	21(42.0%)	

* Significant $p < 0.05$

Table 4. Inheritance pattern related to clinical subtype.

Cases	Observed Frequency			Expected Frequency		
	General pop. (q)	Sibs (s)	Ratio (s/q)	Dominant (1/2q)	Recessive (1/4q)	Multi-factorial (1/√q)
Total	0.7%	39/761 (5%)	7.14	71.43	35.71	11.95
Focal		2/249 (0.8%)	1.14			
Vulgaris		18/226 (8%)	11.43			
Universal		3/51 (5.9%)	8.43			
Acrofacial		16/235 (6.8%)	9.71			

Table 5. Frequency, correlation (r), and heritability (h2 ± SE) of vitiligo cases among relatives of probands.

	n	%	r	h2	SE (%)
1st degree	55/1196	(5.00%)	0.28	55%	0.56
2nd degree	41/1985	(2.07%)	0.15	61%	1.12
3rd degree	46/5848	(0.79%)	0.02	12%	2.25
Weighted mean				54%	1.31

Discussion

Little is known about the genetic nature of vitiligo, although there have been many studies on familial clustering (3, 4, 9, 10) and susceptibility genes (8, 18–23). Previous small-scale studies of genetic modeling of vitiligo were conducted in the United States and India, in which the genetic model for vitiligo was autosomal recessive with 3 or 4 loci controlling the disease. However, the patients' clinical features were unknown in these studies (9, 10).

Our study was carried out on a random sample of vitiligo cases from the Qassim region of Saudi Arabia, emphasizing genetic issues related to this disease. To our knowledge, this study is the first conducted on vitiligo genetics in the Saudi population. This study indicated that vitiligo patients were most commonly affected by the focal subtype followed in order by the vulgaris, acrofacial, and universal subtypes.

Theoretically, consanguineous marriages should carry a high risk for the development of diseases that have a genetic basis, either completely or partially (24, 25). This study showed that about one-third of our cases were positive for a parental consanguinity with a particularly high first-cousin consanguinity that was higher than that reported among the general Saudi population (22.5% vs. 19.5%) (26). First-cousin consanguinity was noted to be particularly high among sufferers of the universal subtype of the disease, followed by acrofacial, vulgaris, and focal subtypes. The consanguinity rate was significantly higher among cases with skin type IV, mucosal and hair involvement, and longer duration of the disease (> 5 years).

Moreover, a positive family history was obtained in 56.8% of families studied, 57.1% of them having two or more affected relatives. A positive family history was noted to be significantly high among cases with the vulgaris and acrofacial subtypes, followed by the universal and focal subtypes. It was also significantly high among cases with skin type IV compared to other cases. Inheritance pattern prediction using the frequency of vitiligo among sibs in relation to the general population coincided more with the multifactorial model especially for the vulgaris subtype followed by the acrofacial subtype, and least in the focal subtype. Calculation of heritability showed a high weighted mean of 0.54. A similar finding was reported by Sun et al. in south China, who found a positive family history in 15.7% and heritability between 55.2% and 59.6%. They concluded that genetic factors play an important role in the occurrence of vitiligo, and the genetic model of vitiligo in this population was consistent with a polygenetic or multifactorial inheritance in a dominant major gene pattern (27). According to the heritabilities reported by previous studies, only half of the phenotypic variance was attributed to genetic factors, and so environmental factors should be taken into account as other causes of vitiligo (10, 28–32).

As seen in this study, the incidence rates of vitiligo in relatives increased with closer blood relationship to probands, which is indicative of the significant familial aggregation of vitiligo noted in a number of previous studies (9, 10). The proband cases we studied showed higher relative risks among their first- and second-degree relatives with a degree significantly greater than unity; but not as high among their third-degree relatives. Frequency among sibs was higher in the vulgaris and acrofacial subtypes than in the universal subtype, and lowest in the focal subtype. The median age of onset was lower for consanguineous cases and cases with a positive family history than other cases. These cases were probably affected by both their genetic backgrounds and common environmental factors. These findings were indicative of a multifactorial cause of vitiligo (33). In addition, Boisseau-Garsaud et al. in the French West Indies observed that the prevalence among relatives of patients was 7%, as compared to 0.34% in the general population ($p < 0.001$). The age of onset of vitiligo was 31 in family cases and 33 in controls. Vitiligo occurred before the age of 20 in 19% of family cases and in 36% of controls. Most families (75%) have no more than two affected members (34).

It is concluded from this study's findings that genetic factors play a relatively important role in the evolution of vitiligo among subjects in the Qassim region with potential impact on disease prevention and family counseling. We also infer that, regardless of a patient's gender, consanguinity and a family history of vitiligo have significant effects on the clinical presentation and age of onset of the disease.

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A U T H O R S' A D D R E S S E S *Abdullateef Alzolibani, MD, Assistant Professor of Dermatology, Department of Dermatology, College of Medicine, Qassim University, Saudi Arabia, P.O. Box 30109, Buraidah 51477, Qassim, Saudi Arabia, Tel Office : +966 6 3800050 ext. 2862, Fax : +966 6 3801228 E-mail : azolibani@yahoo.com*