Consanguinity pattern and heritability of Vitiligo in Arar, Saudi Arabia

Dhaifallah A. Alenizi

Department of Dermatology, College of Medicine, Northern Borders University, Arar, Kingdom of Saudi Arabia

Address for correspondence: Dr. Dhaifallah A. Alenizi, P.O. Box 334, Arar 91411, Kingdom of Saudi Arabia. E-mail: daifallah.alenizi@nbu.edu.sa

Context: Epidemiological studies have shown that vitiligo is a complex trait, involving combinations of pathogenic effects of multiple susceptibility genes as well as environmental risk factors. Aim: To observe whether consanguinity increased the incidence of vitiligo in Saudi patients from Arar. Patients and Methods: This study included 69 Saudi patients with vitiligo and their families. These patients, selected from the experience specialist dermatology center in Arar, from April 2011 to 2012, were interviewed by a dermatologist to confirm the diagnosis and complete a questionnaire. Results: A total of 69 patients, 40 males and 29 females were selected. Their mean age was 34.5 ± 11.8 years with the median age of 23 years. The mean age at onset of disease was 27.9 ± 12.9 years. The mean duration of the disease was 9.7 ± 5.3 years. The frequency of focal, vulgaris, universal, and acrofacial subtypes was 22 (31.9%), 21 (30.4%), 8 (11.6%), and 18 (26.1%), respectively. A positive family history of vitiligo was obtained in 45 (65.2%) cases. A comparison of the frequency of vitiligo among siblings in relation to the general population was more in accord with the multifactorial model. Conclusion: Consanguinity in marriage increases the incidence of the disease. Therefore, genetic counseling and premarital examination would be important contributions to lower the prevalence of vitiligo.

Key words: Arar, consanguinity pattern, genetic, vitiligo

INTRODUCTION

Vitiligo is a complex disorder in which acquired progressive, multifocal loss of pigmentation of skin, and hair results from the loss of melanocytes from the affected areas.[1] Although several theories have been proposed about the pathogenesis of vitiligo, the precise cause remains unknown. Theories on the destruction of melanocytes include autoimmune mechanisms,[2] cytotoxic mechanisms, an intrinsic defect of melanocytes, oxidant-antioxidant mechanisms, and neural mechanisms.[3]

Because of its visually striking phenotype, vitiligo has been recognized for thousands of years.[4] Epidemiological studies have shown that vitiligo is a complex trait, involving combinations of pathogenic effects of multiple susceptibility genes and environmental risk factors. Clustering of vitiligo cases occurs in some families, almost always in non-Mendelian patterns, indicative of polygenic, multifactorial causation.[5,6] Indeed, the concordance of vitiligo in monozygotic twins is only 23%, highlighting the importance of environmental triggers, which as yet remain unknown.[7]

Aim of the study

The aim of this study was to discover whether consanguinity increased the incidence of vitiligo in Saudi patients from Arar (on the northern borders area), an area where there is a high incidence of the condition in families.

MATERIALS AND METHODS

This study consisted of 69 Saudi patients with vitiligo and their families. These patients were selected from the experience specialist dermatology center in Arar, from
April 2011 to April 2012. The patients were interviewed by a dermatologist to confirm the diagnosis and complete the questionnaire which had the following items: Age, sex, age of onset, clinical classification, and course of the disease. Also information about first degree relation, that is, close blood relative such as the individual’s parents, full siblings, or children, second degree, that is, a blood relative such as the individual’s grandparents, grandchildren, aunts, uncles, nephews, nieces, or half-siblings; and third degree blood relations including the individual’s first-cousins, great-grandparents, or great grandchildren, and also the number of vitiligo cases among relatives. A verbal consent was obtained from the patients who were also informed that the data were being collected for scientific purposes and would remain confidential.

Statistical analysis was done using SPSS 20; quantitative data were expressed in mean and standard deviation, and qualitative data were expressed in number and percentage. Intergroup comparison was done using Chi-square test (X²) and z test for proportion to compare number and percentage in two numbers from the same group. Inbreeding coefficients were calculated by the Fraser and Mayo formula. The observed relative frequency (s/q) was estimated by dividing frequency in the siblings (s) by the 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. P < 0.05 is considered significant.

RESULTS

Of the 69 patients selected, 40 were males and 29 females. Their mean age was 34.5 ± 11.8 years with a median of 23 years. The mean age of the onset of the disease was 27.9 ± 12.9 years; the mean duration of the disease was 9.7 ± 5.3 years [Table 1].

The frequency of focal, vulgaris, universal, and acrofacial subtypes was 22 (31.9%), 21 (30.4%), 8 (11.6%), and 18 (26.1%), respectively.

A positive family history of vitiligo was present in 45 (65.2%) cases, which is statistically significantly higher [Table 2]. Parental consanguinity was shown in 28 (40.6%) cases. Particularly high first cousin consanguinity (27.5%) resulted in a relatively high coefficient of inbreeding of 0.018 [Table 3].

Table 4 shows that consanguinity was statistically significantly higher in those with skin type IV than those with skin type III (P = 0.03) and there was no statistically significant difference between the three groups [negative, first cousin, and others] as regards clinical subtypes, mucosal involvement, white hair, and duration of the disease.

Table 5 illustrates the relation between family history and clinical subtypes, mucosal involvement, white hair, skin type, and duration of the disease. There was statistically significant difference between positive and negative family history as regards both clinical subtypes and skin subtype. The positive family history was higher in acrofacial (94.4%), followed by vulgaris (85.7%) by the universal (50%) followed by focal type (27.3%) (P < 0.001). As regard to skin type, a positive family history was statistically significantly higher in type IV (P = 0.03). There was no statistically significant difference as regards mucosal involvement, white hair, and duration of the disease.

Table 6 indicates that a comparison of the frequency of vitiligo among siblings in relation to the general population reveals an inheritance pattern more coincident with the multifactorial model especially for the vulgaris (11.7%) subtype, followed by the universal (8.9%), acrofacial (8.1%), and focal subtypes (1.5%).

DISCUSSION

Vitiligo is an acquired, idiopathic, worldwide common depigmentation disorder with an estimated prevalence...
Consanguinity pattern and heritability of vitiligo

The most important recent developments in vitiligo occurred in two large-scale genome wide association studies of generalized vitiligo, one in Caucasians\[10\] and the other in Chinese, \[11\] which together identified and confirmed at least 16 different loci that contribute to the susceptibility of generalized vitiligo.

This current study done on a sample of vitiligo cases from Arar [northern borders area, Kingdom of Saudi Arabia (KSA)] confirmed the role of the genetic factor in the development of this disease.

It indicated that focal subtype of vitiligo was the most common followed by vulgaris then acrofacial and universal subtypes.

The higher incidence of consanguineous marriages in our part of the world increases the importance of associated genetic factors in any given disease.\[12\] This study showed that 40.6% of the cases showed parental consanguinity which was higher in first cousins (27.5%) clinical subtypes in first cousins was arranged in this order. First came, the universal followed by acrofacial, vulgaris, and finally focal.\[13\]

In this study, the positive family history cases (65.2%) was significantly higher than the negative family history ones (34.8%). This is in agreement with Zamani et al.,\[14\]

### Table 4: Consanguinity pattern related to clinical subtype

| Parameter                | Negative (%) | First cousin (%) | Others (%) | X²  | P   |
|--------------------------|--------------|------------------|------------|-----|-----|
| **Clinical subtypes**    |              |                  |            |     |     |
| Focal                    | 15 (68.2)    | 5 (22.7)         | 2 (9.1)    | 6.6 | 0.36|
| Vulgaris                 | 13 (61.9)    | 6 (28.6)         | 2 (9.5)    |     |     |
| Universal                | 2 (25)       | 3 (37.5)         | 3 (37.5)   |     |     |
| Acrofacial               | 11 (61.1)    | 5 (27.8)         | 2 (11.1)   |     |     |
| **Mucosal involvement**  |              |                  |            |     |     |
| Positive                 | 8 (66.6)     | 2 (16.7)         | 2 (16.7)   | 0.89| 0.63|
| Negative                 | 33 (57.9)    | 17 (29.8)        | 7 (12.3)   |     |     |
| **White hair**           |              |                  |            |     |     |
| Positive                 | 4 (50)       | 2 (25)           | 2 (25)     | 1.1 | 0.56|
| Negative                 | 37 (60.6)    | 17 (27.9)        | 7 (11.5)   |     |     |
| **Skin type**            |              |                  |            |     |     |
| Type III                 | 10 (100)     | 0 (0)            | 0 (0)      | 7.1 | 0.03*|
| Type IV                  | 33 (55.9)    | 18 (30.5)        | 8 (13.6)   |     |     |
| **Duration**             |              |                  |            |     |     |
| ≤5 years                 | 24 (64.68)   | 10 (27.03)       | 3 (8.11)   | 1.9 | 0.39|
| >5 years                 | 17 (53.13)   | 9 (28.13)        | 6 (18.75)  |     |     |

### Table 5: Family history related to clinical subtype, mucosal, and hair involvement and disease severity

| Parameter                  | Family history (%) | X²  | P     |
|---------------------------|--------------------|-----|-------|
| **Clinical subtypes**      |                    |     |       |
| Focal (22)                | 6 (27.3)           | 25.4| <0.001**|
| Vulgaris (21)             | 18 (85.7)          | 3 (14.3) |     |       |
| Universal (8)             | 4 (50)             | 4 (50) |     |       |
| Acrofacial (18)           | 17 (94.4)          | 1 (5.6) |     |       |
| **Mucosal involvement**   |                    |     |       |
| Positive (12)             | 9 (75)             | 0.6 | 0.4   |
| Negative (57)             | 36 (63.2)          | 21 (36.8) |     |       |
| **White hair**            |                    |     |       |
| Positive (8)              | 5 (62.5)           | 0.1 | 0.8   |
| Negative (61)             | 40 (65.6)          | 21 (34.4) |     |       |
| **Skin type**             |                    |     |       |
| Type III (10)             | 3 (30)             | 7 (70) | 4.7   | 0.03* |
| Type IV (59)              | 42 (71.2)          | 17 (28.8) |     |       |
| **Duration**              |                    |     |       |
| ≤5 years (37)             | 21 (56.8)          | 16 (43.2) | 2.5  | 0.1   |
| >5 years (32)             | 24 (75)            | 8 (25)  |     |       |

The results of the genetic studies thus far show that generalized vitiligo is a typical polygenic, multifactorial disorder, involving numerous different susceptibility genes, and that the great majority of these genes encode proteins that regulate or mediate recognition or destruction of melanocytes by the immune system.\[9\]
and some other studies\textsuperscript{5,13,15} which found vitiligo to be strongly associated with family history of the condition. A positive family history was significantly higher in cases with acrofacial and vulgaris subtype, followed by universal and focal subtypes. Family history was also significantly higher in type IV skin type compared to those with a negative family history. This is similar to Shekokar and Ghubde\textsuperscript{16} who stated that vitiligo occurred more commonly in blood relatives. It is also similar to the findings of Tanioka \textit{et al.},\textsuperscript{17} who stated that family members were predisposed to vitiligo itself. They found that significant family inheritance presented itself as an appreciable factor for this disease. Chromosomal changes, for example, metaphase were evident in half of cases. Environmental factors should also be borne in mind as a cause or a trigger for the occurrence of vitiligo.\textsuperscript{9}

### CONCLUSION

This study would help to alert the population to the consequences of consanguinity and its potential to increase the incidence of diseases such as vitiligo in which genetics play a role. Genetic counseling and premarital examination are, therefore, important means by which the prevalence of vitiligo can be reduced.

### ACKNOWLEDGMENT

To all workers in the experience specialist centre.

### REFERENCES

1. Spritz RA. The genetics of generalized vitiligo: Autoimmune pathways and an inverse relationship with malignant melanoma, Genome Med 2010;2:78.
2. Le Poole IC, Luiten RM. Autoimmune etiology of generalized vitiligo. Curr Dir Autoimmun 2008;10:227-43.
3. Spritz RA. The genetics of generalized vitiligo. Curr Dir Autoimmun 2008;10:244-257.
4. Nordlund JJ, Ortonne JP, Le Poole IC. Vitiligo vulgaris. In: Nordlund JJ, Boissy RE, Hearing VJ, King RA, Oetting WS, Ortonne JP, editors. The Pigmentary System 2. Oxford: Blackwell Press; 2006. pp. 551-98.
5. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res 2003;16:208-14.
6. Laberge G, Mailloux CM, Gowan K, Holland P, Bennett DC, Fain PR, \textit{et al}. Early disease onset and increased risk of other autoimmune diseases in familial generalized vitiligo. Pigment Cell Res 2005;18:300-5.
7. Poojary SA. Vitiligo and associated autoimmune disorders: A retrospective hospital-based study in Mumbai, India. Allergol Immunopathol 2011;39:53-56.
8. Krüger C, Schallreuter KU. A review of the worldwide prevalence of vitiligo in children/adolescents and adults. Int J Dermatol 2012;51:1206-12.
9. Spritz R. The Genetics of Vitiligo. J Invest Dermatol 2011;131:E18-20.
10. Jin Y, Birlea SA, Fain PR, Gowan K, Riccardi SL, Holland PJ, \textit{et al}. Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. New Engl J Med 2010;362:1686-97.
11. Quan C, Ren YQ, Xiang L, Sun LD, Xu AE, Gao XH, \textit{et al}. Genome-wide association study for vitiligo identifies susceptibility loci at 6q27 and the MHC. Nat Genet 2010;42:1617-24.
12. Al-Mutairi N, Al-Sebeih KH. Late onset vitiligo and audiological abnormalities: Is there any association? Indian J Dermatol Venereol Leprol 2011;77:571-6.
13. Alzolibani A. Genetic epidemiology and heritability of vitiligo in the Qassim region of Saudi Arabia. Acta Dermato-Venereol Alp Panon Med 2010;36:249-57.
14. Zamani M, Spaepen M, Sghar SS, Huang C, Westerhof W, Nieuweboer-Krobotova L, \textit{et al}. Linkage and association of HLA class II genes with vitiligo in a Dutch population. Br J Dermatol 2001;145:90-4.
15. Pajvani U, Ahmad N, Wiley A, Levy RM, Kundu R, Mancini AJ, \textit{et al}. The relationship between family medical history and childhood vitiligo. J Am Acad Dermatol 2006;55:238-44.
16. Shekokar A, Ghubde R. Pedigree Analysis and Cytogenetic Study in Vitiligo. J Clin Diagn Res 2011;5:929-31.
17. Tanioka M, Yamamoto Y, Katoh M, Takahashi K, Miyachi Y. Vitiligo vulgaris and autoimmune disease in Japan. A report from vitiligo clinic in Kyoto University Hospital. Dermatoendocrinol 2009;1:43-5.

How to cite this article: Alenizi DA. Consanguinity pattern and heritability of Vitiligo in Arar, Saudi Arabia. J Fam Community Med 2014;21:13-6.

Source of Support: Nil, Conflict of Interest: None declared.