

Review

Worldwide distribution of HLA-B27 and Behcet Disease: a systematic review and meta-analysis

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Abstract: *Objective* — Performing global population-based studies and comparing the results with other studies can reveal regional differences in the distribution of HLA-B27 in patients with Behcet disease. The aim of study was reviewing the distribution of HLA-B27 and Behcet disease in the world.

Material and Methods — A systematic review search was conducted of the MeSH keywords of Behcet disease, HLA-B27 and B27 in ProQuest, Scopus, EMBASE, SID, IranDoc and IranMedex from 1975 to 2017 in Iran. Data was analyzed using meta-analysis (random effect model) in Software CMA2. The heterogeneity of studies was assessed with I^2 index.

Results — The pooled frequency of HLA-B27 in patients with patients throughout the world for 11,483 samples and 36 studies was 7.4%. A higher frequency of HLA-B27 was found in Europe for, followed by the Middle East (7.2 (4.5-11.7)%, $P<0.001$) and Far East (6.4 (2.1-19.4)%, $P<0.001$). By country, the highest frequency was found for Great Britain 16.7% (8.6-33.1), followed by Iran 7.2% (4.5-11.7) and Turkey 5.9 (3.6-9.9)%.

Conclusion — The results demonstrate the role of HLA-B genes such as -B27 on Behcet disease and provide information about the causes and effects of the subject to help design health programs and carry out future investigations on the odds ratio.

Keywords: Behcet disease, HLA-B27, Distribution

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Introduction

Behcet disease (BD) is a vascular autoimmune disease [1] which is characterized by recurrent oral ulcers, genital ulcers, skin lesions and ocular involvement [2]. BD has been frequently reported in the Mediterranean basin and Far East between 30° and 45° N latitude and was spread along the ancient Silk Road by migrating Turks [3, 4]. Today, BD has been observed in Europe, America and Oceania [3, 4]. The etiology of this disease is unknown, but genetic and environmental factors play an important role in its emergence [3, 4]. Human leukocyte antigen (HLA) class I alleles, especially HLA-B51, is strongly associated with BD [4, 5]; however, it expresses a marker for other genes in linkage disequilibrium (LD) with it [3, 4, 6]. The major histocompatibility complex (MHC), a group of genes that code proteins found on the surfaces of cells, is essential for the acquired immune system that is known in humans as the HLA [3, 4, 6]. Recent investigations have compared HLA-B27 in different populations and ethnicities with various clinical manifestations of BD [5, 7]. Although the diagnosis of BD is based on clinical presentation, HLA markers may be significant in the diagnosis and prognosis of the disease [8].

Understanding the prevalence, distribution and population influence of HLA-B27 is important for health care planning. Demographic and population studies have focused on size,

distribution, migration, composition and socioeconomic factors. The results of these studies have been applied to government decision-making and analysis of the causes and outcomes of population change [9].

Although there have been studies on HLA-B51 in BD around the world, none have systematically compared the pooled frequency of HLA-B27 in different geographical regions.

To address this gap, the present research undertook a systematic review of published studies to evaluate the frequency of HLA-B27 in BD patients as primary aim and Behcet Disease as secondary aim among continents and countries for the design of health programs and in preparation of future research.

Material and methods

Inclusion and exclusion criteria

This study was a systematic review and meta-analysis of all cross-sectional studies which evaluated the frequency distribution of HLA-B27 in BD between January 1975 and February 2017 according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and PICO approach [10] (participants: patients with BD; interventions: genetic background for HLA-B27; comparison and outcome: None) [11]. Moreover, due to the

rareness of BD in some areas, a number of articles were also included that did not conform to the PRISMA checklist to allow coverage of specific items in the results.

The inclusion criteria consisted of all subtypes of HLA-B27 with or without concomitance with other types of HLA and all ages, sexes, countries and ethnicities as well as without language limitation. The exclusion criteria were studies reporting on animal studies, case reports, case series, letters, clinical trials and disagreements between reviewers, as well as studies in which a subset of BD patients (uveitis and arthritis) were excluded.

Search strategy

PubMed, ProQuest, Scopus, EMBASE, SID (Scientific Information Database), IranDoc (Iranian Research Institute for Information Science and Technology), Magiran and IranMedex were searched by combining MeSH keywords of Behcet disease, Behcet's syndrome, HLA-B27, B27, Frequency and their combinations. References of the related reviewed studies were surveyed manually. Unpublished studies and "gray" literatures (such as studies presented at congresses or working papers) were searched. In the case of unpublished studies or ambiguous data, we contacted the authors for more information.

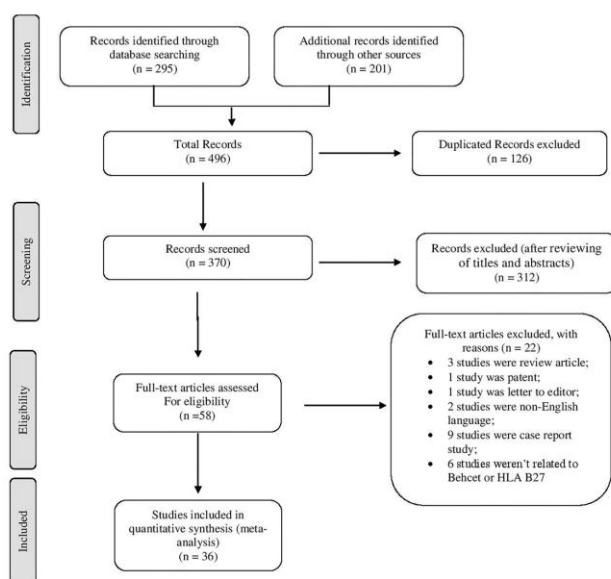


Figure 1. Flow diagram of trials for inclusion in the systematic review and meta-analysis.

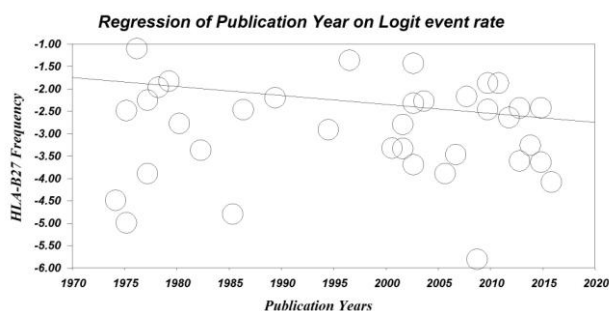


Figure 2. Meta-Regression based on the date of publication.

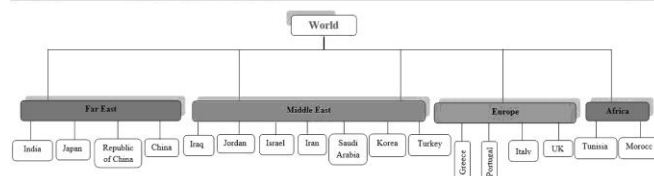
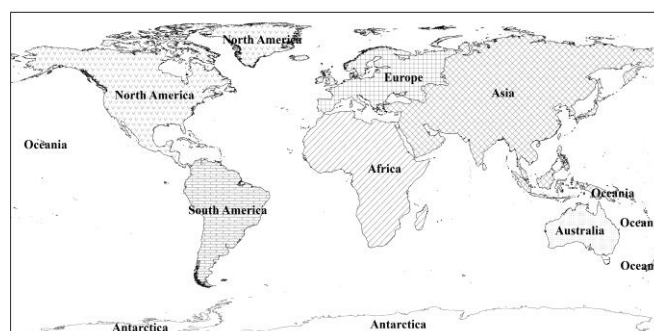


Figure 3. A neighbor-joining tree (dendrogram) and Geographical map for Behcet's disease based on countries and continent.

Selection process

Each paper was independently controlled by two reviewers (K.A and V.L). Any disagreements between the two reviewers were solved by the third reviewer (G.M). The article is excluded if it did not get credit score from the third reviewer. The Kappa agreement rate was higher than 85%.

Data extraction and data analysis

The variables which were extracted from the articles were the name of the first author, publication date and location of the study, sample size and frequency of the HLA-B27 antigen summarized in extracted form. The continents were divided to five groups, including Far East, Middle East, Europe, Africa and America. The Turkey was categorized in the Middle East.

The systematic review was surveyed at by least two appraisers. The frequency, percentage and ratio were used as definite variables. Endnote X5 was used to organize the data, review the titles and abstracts and identify duplicated studies. A funnel plot was used to check for the existence of publication bias. It should be mentioned, at the beginning of the meta-analysis, logarithmic transformation was carried out for the frequency of HLA-B27, due to close to zero this value in a number of articles. Thus, the forest plot has been reported based on negative numbers following this logarithmic transformation.

The meta-analysis was performed using a random effect model for $I^2 > 50$ or $p < 0.05$. The pooled event rate was calculated to determine the frequency of HLA-B27 in BD-patients. Heterogeneity between studies was calculated by Cochran's Q and I^2 tests to examine the percentage of changes between studies using the software CMA v.2.0 (Biostat Inc, USA) [12]. The results of the meta-analysis are presented as forest plots. Results were considered significant at $P < 0.05$.

Ethical subject

This study has been conducted at the Connective Tissue Disease Research Center (CTDR) in Tabriz University of Medical Sciences (Tabriz, Iran). All data were kept stating the name of patients and addresses.

Table 1. Frequency of HLA-B27 in Behcet disease based on Logit event rate, lower limit to upper limit

Continent	Authors	Event Rate (log)	Lower limit to Upper limit	Z value	P-value
Far East	Pande I (1995)	-2.90	(-4.07) to (-1.74)	-4.90	<0.001
	Takano M. et al (1976)	-4.99	(-7.77) to (-2.20)	-3.50	<0.001
	Ohno S. et al (1975)	-4.48	(-7.27) to (-1.70)	-3.10	0.002
	Chung Y-M. et al (1987)	-2.46	(-3.48) to (-1.44)	-4.70	<0.001
	Cibo H. et al (1997)	-1.35	(-2.09) to (-0.62)	-3.60	<0.001
	Subtotal	-2.73	(-3.83) to (-1.63)	-4.80	<0.001
Middle East	Rawi Z. et al (1986)	-4.79	(-7.57) to (-2.01)	-3.30	0.001
	Mustafa TAA (2003)	-1.42	(-1.87) to (-0.98)	-6.20	<0.001
	Brautbar C. et al (1978)	-3.89	(-6.69) to (-1.09)	-2.70	0.006
	Xavier JM. et al (2015)	-3.63	(-4.03) to (-3.23)	-17.90	<0.001
	Fatemi A. et al (2015)	-2.42	(-2.72) to (-2.12)	-15.90	<0.001
	Chams-Davatchi C. et al (2003)	-2.32	(-3.24) to (-1.40)	-4.90	<0.001
	Amirzargar A. et al (2010)	-1.87	(-2.73) to (-1.01)	-4.20	<0.001
	Davatchi F. et al (2010)	-2.46	(-2.55) to (-2.37)	-53.40	<0.001
	Al-Okaily F. et al (2016)	-4.07	(-6.05) to (-2.10)	-4.04	<0.001
	Chang HK. et al (2002)	-2.79	(-3.95) to (-1.62)	-4.60	<0.001
	Moon S-J. et al (2013)	-2.42	(-3.60) to (-1.24)	-4.03	<0.001
	Yazici H. et al (1980)	-1.82	(-2.76) to (-0.88)	-3.70	<0.001
	Muftuocl AU. et al (1981)	-2.77	(-3.53) to (-2.00)	-7.10	<0.001
	Gul A. et al (2002)	-3.33	(-4.14) to (-2.51)	-8.02	<0.001
	Pirim I. et al (2004)	-2.27	(-3.05) to (-1.49)	-5.70	<0.001
	Mizuki N. et al (2007)	-3.46	(-5.45) to (-1.47)	-3.40	0.001
	Ombrelloa MJ (2014)	-3.26	(-3.56) to (-2.95)	-21.20	<0.001
	Subtotal	-2.65	(-2.98) to (-2.32)	-15.75	<0.001
Europe	Zouboulis CC. et al (2003)	-3.68	(-5.09) to (-2.28)	-5.10	<0.001
	Munoz-Saa I. et al (2006)	-3.89	(-6.69) to (-1.09)	-2.70	0.006
	Montes-Cano MA. et al (2013)	-3.61	(-4.31) to (-2.90)	-10	<0.001
	Bettencourt A. et al (2008)	-2.16	(-2.90) to (-1.43)	-5.80	<0.001
	Piga M. et al (2012)	-2.63	(-3.81) to (-1.46)	-4.40	<0.001
	Olivieri I. et al (1990)	-2.19	(-3.65) to (-0.73)	-2.90	0.0030
	Chamberlain MA (1978)	-2.25	(-3.70) to (-0.79)	-3.02	0.0020
	Lehner T. et al (1979)	-1.96	(-2.70) to (-1.22)	-5.20	<0.001
	Caporn BN. et al (1983)	-3.36	(-6.18) to (-0.54)	-2.30	0.010
	Chamberlain MA (1977)	-1.09	(-1.95) to (-0.24)	-2.51	0.010
	Subtotal	-2.51	(-3.10) to (-1.80)	-7.93	<0.001
	Sakly N. et al (2009)	-5.80	(-8.57) to (-3.02)	-4	<0.001
Africa	Radouane A. et al (2011)	-1.87	(-2.39) to (-1.34)	-6.90	<0.001
	Choukri F. et al (2001)	-3.32	(-4.47) to (-2.16)	-5.60	<0.001
	Subtotal	-3.20	(-4.91) to (-1.50)	-3.60	<0.001
America	O'Duffy JD. et al (1976)	-2.48	(-3.92) to (-1.04)	-3.30	0.001

Results

In the systematic review, 496 articles were identified. Of these, 126 were excluded as duplicates, 312 studies were excluded after initial title and abstract reviews and 22 were excluded after full text review. A final total of 36 articles fulfilled the inclusion criteria as shown in the flow chart of search articles in *Figure 1*.

Data from BD patients in the Far East, Middle East, Europe, Africa and America were pooled separately. The analysis showed the overall heterogeneity among continents and countries where $I^2 > 60\%$ expectation of UK is shown in *Table 1*. The pooled overall frequency of HLA-B27 in BD patients globally was 7.4% [(CI 95% 5.8-9.4), $P < 0.001$] for a total of 11,483 samples (*Table 2*).

The results showed the pooled frequency of HLA-B27 was more common in European than in the Middle East, Far East and Africa, which suggests a difference among regions. Comparison among countries indicates that the UK had higher combined HLA-B27 than Iran and Turkey (*Table 1*). The higher pooled frequency of HLA-B27 was related to Chamberlain MA in UK [13]. Moreover, Middle East populations had a higher BD patient rate than others and results showed similar samples among subgroups.

Up to the year 2000, the overall frequency of BD patients, HLA-B27 and articles were calculated 683 (6%), 49 (6%) and 15 (30%), while these items, after the year 2000 were calculated 10800 (94%), 723 (94%) and 36 (70%), respectively. Indeed, it indicates increasing the number of BD patients and improving the detection of the

pathogenic mutations in deoxyribonucleic acid (DNA). Comparison between continents showed further reports has been published in the Far East before 2000 year and in Africa after this year.

A meta-regression was performed based on the date of publication. Meta-regression results showed that the HLA-B27 frequency decreases by 2% per year ($P < 0.001$) (*Figure 2*).

Furthermore, ArcGIS Version-9.3 mapping software as a geo-referenced digital map was used for analyzing and depicting geographic and mapped information in a database. A neighbor-joining tree (dendrogram) has been drawn for country and continents (*Figure 3*).

Discussion

BD is a common autoimmune disease globally [14] with multifactorial pathogenesis such as genetic factors play a critical role. There is a strong correlation between BD and human MHC [3]. This systematic review and meta-analysis was carried out to investigate the distribution of HLA-B27 in BD and Behcet Diseases in subgroups as defined by continents and countries. To the best of our knowledge, this is the first study was conducted on the distribution of B27 and Behcet's Disease.

The current study has shown that the HLA-B27 frequency was 7.4% in BD patients and the number of individuals affected by BD was 11,483 cases.

Table 2. Characteristics of articles related to HLA-B27 in Behcet disease across the world

Continents	Authors	Places	Cases N=36 Papers		Pooled rate Effect size and 95% confidence interval	Heterogeneity		
			Sample Size F (%) (Case)	HLA-B27 F (Case)		df (Q)	P-value	I ²
Far East	Pande I (1995) [28]	India	58 (0.5)	3	-	-	-	-
	Takano M. et al (1976) [29]	Japan	73 (0.6)	0	-	-	-	-
	Ohno S. et al (1975) [30]	Japan	44 (0.4)	0	-	-	-	-
	Chung Y-M. et al (1987) [31]	China	51 (0.4)	4	-	-	-	-
	Cibo H. et al (1997) [32]	China	44 (0.4)	9	-	-	-	-
	<i>Subtotal</i>		270 (2.4)	16	6.4 (2.1-19.4)%, P<0.001	4	0.010	69.69
	Rawi Z. et al (1986) [33]	Iraq	60 (0.5)	0	-	-	-	-
	Mustafa TAA (2003) [34]	Jordan	124 (1.1)	24	-	-	-	-
	Brautbar C. et al (1978) [35]	Israel	24 (0.2)	0	-	-	-	-
	Xavier JM. et al (2015) [36]	Iran	973 (8.5)	25	-	-	-	-
Middle East	Fatemi A. et al (2015) [37]	Iran	577 (5.0)	47	7.2% (4.5-11.7), P<0.001	4	<0.001	88.42
	Chams-Davatchi C. et al (2003) [14]	Iran	56 (0.5)	5	-	-	-	-
	Amirzargar A. et al (2010) [38]	Iran	45 (0.4)	6	-	-	-	-
	Davatchi F. et al (2010) [39]	Iran	6500 (56.6)	511	-	-	-	-
	Al-Okaily F. et al (2016) [40]	Saudi Arabia	60 (0.5)	1	-	-	-	-
	Chang HK. et al (2002) [41]	Korea	52 (0.5)	3	-	-	-	-
	Moon S-J. et al (2013) [42]	Korea	37 (0.3)	3	-	-	-	-
	Yazici H. et al (1980) [43]	Turkey	36 (0.3)	5	-	-	-	-
	Muftuoc AU. et al (1981) [44]	Turkey	119 (1)	7	-	-	-	-
	Gul A. et al (2002) [19]	Turkey	174 (1.5)	6	5.9 (3.6-9.9)%, P<0.001	5	0.021	62.34
Europe	Pirim I. et al (2004) [15]	Turkey	75 (0.7)	7	-	-	-	-
	Mizuki N. et al (2007) [18]	Turkey	33 (0.3)	1	-	-	-	-
	Ombrello MJ (2014) [45]	Turkey	1190 (10.4)	44	-	-	-	-
	<i>Subtotal</i>		10135 (88.3)	695	7.0 (5.0-9.8)%, P<0.001	16	<0.001	83.09
	Zouboulis CC. et al (2003) [46]	Greece	82 (0.7)	2	-	-	-	-
	Munoz-Saa I. et al (2006) [47]	Spain	24 (0.2)	0	-	-	-	-
	Montes-Cano MA. et al (2013) [48]	Spain	304 (2.6)	8	-	-	-	-
	Bettencourt A. et al (2008) [49]	Portugal	78 (0.7)	8	-	-	-	-
	Piga M. et al (2012) [50]	Italy	45 (0.4)	3	-	-	-	-
	Olivieri I. et al (1990) [51]	Italy	20 (0.2)	2	-	-	-	-
Africa	Chamberlain MA (1978) [52]	UK	28 (0.2)	7	-	-	-	-
	Lehner T. et al (1979) [53]	UK	65 (0.6)	8	16.7 (8.6-33.1)%, P<0.001	3	0.200	29.63
	Caporn BN. et al (1983) [54]	UK	14 (0.1)	0	-	-	-	-
	Chamberlain MA (1977) [13]	UK	21 (0.2)	2	-	-	-	-
	<i>Subtotal</i>		681 (5.9)	40	8.0 (4.3-15.0)%, P<0.001	9	0.001	66.69
	Sakly N. et al (2009) [7]	Tunisia	165 (1.4)	0	-	-	-	-
	Radouane A. et al (2011) [55]	Morocco	120 (1.0)	16	-	-	-	-
	Choukri F. et al (2001) [56]	Morocco	86 (0.7)	3	-	-	-	-
	<i>Subtotal</i>		371 (3.2)	19	4.0 (0.7-22.1)%, P<0.001	2	0.003	82.73
	O'Duffy JD. et al (1976) [57]	USA	26 (0.2)	2	-	-	-	-
America								
Total			11483 (100)	772	7.4% (5.8-9.5), P<0.001	35.00	<0.001	76.67

The pooled frequency of HLA-B27 in BD patients was greater in Europe, followed by the Middle East, Far East and Africa. Among countries, the UK ranked first, followed by Iran and Turkey. The highest number of samples has been recorded in the Middle East, especially Iran, and the proportion in other continents and countries was similar or lower. Previous meta-analyses have reported on the strong correlation between HLA-B51 and BD, but the current analysis suggests the necessity of investigation of B27 in BD [6, 15, 16]. Likewise, Gül believed that, despite the strong association of HLA-B51 with BD, there is controversy about this association due to a role of the MHC class I variants [17].

It is not known whether HLA-B51 is a BD susceptibility gene itself or if this strong association displays linkage disequilibrium with another gene or other HLA-B genes [16, 17].

BD is known as the Silk Road disease because it spread along that ancient and historical route from the Far East (Japan, Korea,

China) to the Mediterranean basin (Turkey, Tunisia, Morocco) [3, 4]. On the other hand, -B51 frequency was observed first in Arabs, Turks and Jews and in the Far East [6]. According to reported papers, the geographical distribution of genes, such as HLA-B51 or others at near it, is potentially related to the global distribution of BD [18, 19]. This distribution is more solid in B51, because of it's strongly association. In this study, the distribution of HLA-B51 differs slightly with BD. Nonetheless, the pool of BD in peoples carrying a high frequency of HLA-B51 could relate to the fact that genetic susceptibility to BD is secondary either to HLA-B51 subtypes or to genes near LD with HLA-B51 [6].

Today, HLA-B27 is a subject of study in medicine as related to the pathogenesis of diseases such as BD. This antigen has several subtypes with variety frequencies, distributions and clinical manifestations in different populations and ethnicities due to impression other MHC and non-MHC genes [20]. This systematic

review highlights the role of B27 and other factors. A higher pooled frequency of HLA-B27 was found from the data in Europe than in other places.

The spread of HLA-B27 and BD in Europe, especially in the UK was an interesting finding of this study. The UK has invested in molecular diagnostic techniques and the management of information. The improvement in molecular diagnosis and recording information from sources such as hospitals, laboratories and medical clinics could justify this alternation.

Of notes, a review study reported that BD is prevalent in the Middle East, followed by the Far East, North Africa, Europe, the USA and Australia because it was spread by human migration along the Silk Road from the Far East to the West [6]. The Silk Road contributed strongly to the spread between the East and West because of the economic, political, religious, and cultural exchange that elevated immigration from East to West [21]. Therefore, this finding relates to the number of Asian migrants to these places. The proximity of Europe to the Mediterranean region and increased migration between these areas has increased the gene flow and the spread a number of diseases. It is likely that genetic diversity and some types of disease in Europe and even America are associated with these events [22]. It is suggested that this disease was spread by Turks from northern China to Iran, Turkey, Europe, Africa and America [23].

A founder effect can occur during migration. This can result in genetic isolation and inter-ethnic marriage that allows the frequency of the allele for BD to persist and increase over time [24]. America has been exposed to these changes at much lower rate.

It is possible that the emergence of BD has declined due to random events such as genetic drift [25], Bottleneck effect [26] environmental factors [27] and failure to report. Moreover, it is likely that BD cases with other backgrounds have been seen in these regions and it is necessary to carry out further investigation.

The difference in the frequency of disease and related genes should be investigated in demographic studies among immigrants. Takeuchi et al. determined that the frequency of BD among Turkish immigrants dropped to less than the Turkish people, but was more than in Germans [16].

Strength and Limitation

The advantage of the current study is the use of pooled data for analysis and, for the first time, different geographical regions were compared for HLA-B27 subject to BD.

This study was limited by incomplete information that prevented subgroup analysis for sex and age. Ultimately, this study surveyed the incidence of BD with a HLA-B27 background. Analysis of HLA-B27 frequency independent of HLA-B51, in a subset of BD or in control and cases groups is recommended.

Conclusion

The results show the pathogenic role of other HLA-B genes, such as B27, on BD in addition to HLA-B51. A higher frequency of HLA-B27 in Europeans in Asia and Africa has been documented. To determine a possible higher frequency of patients in the Middle East than in Europe and Africa and using more publications from the Far East to up to the year 2000, several hypotheses could be considered, including the effect of migration, other genetic factors, environmental factors, improvement in the detection of

pathogenic mutations in DNA and increased reporting. Moreover, identification of the geographical distribution and how different causes can effect healthcare system planning and government decisions such as implementation of BD care programs or the design of molecular diagnostic kits should be considered. Other studies comparing the frequency HLA-B27 between BD patients and controls and the determination of pooled frequency of HLA-B27 independent of HLA-B51 are needed.

Conflict of interest: none declared.

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