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Original article

Relationships of *HLA-B51* or *B5* genotype with Behçet's disease clinical characteristics: systematic review and meta-analyses of observational studies

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Abstract

Objective. To investigate comprehensively the relationships between Behçet's disease (BD) clinical features and *HLA-B51* or *HLA-B5* (*HLA-B51/B5*) status using meta-analyses.

Methods. Relevant publications were identified by a systematic literature search. Eligible studies had to provide frequencies for one or more BD characteristics according to *HLA-B51/B5* status. Pooled relative risks (RRs) were calculated by random-effects meta-analysis for those BD characteristics for which five or more relevant studies were identified. Between-study variability was assessed with I^2 and *Q*-statistics, and modelled using meta-regression.

Results. Among the 859 publications evaluated, 72 (representing 74 study populations) met eligibility criteria. Pooled RRs (95% CIs) of the association of *HLA-B51/B5* with the 14 analysed clinical characteristics were male sex 1.14 (1.05, 1.23); eye involvement 1.13 (1.06, 1.21); genital ulcers 1.07 (1.01, 1.14); skin involvement 1.10 (1.03, 1.16); erythema nodosum 1.11 (0.96, 1.29); pseudofolliculitis 1.07 (0.93, 1.23); positive pathergy test 1.05 (0.94, 1.17); joint involvement 0.94 (0.86, 1.04); neurological involvement 0.95 (0.71, 1.27); gastrointestinal involvement 0.70 (0.52, 0.94); thrombophlebitis 1.17 (0.77, 1.76); vascular involvement 1.00 (0.68, 1.47); chest involvement 1.55 (0.75, 3.20) and orchiepididymitis 1.13 (0.59, 2.15). For most of the analysed outcomes, between-study heterogeneity was low or absent and most of the meta-regression models were statistically non-significant.

Conclusion. The results of these meta-analyses showed that, in BD, *HLA-B51/B5* carriage predominates in males and is associated with moderately higher prevalences of genital ulcers, ocular and skin manifestations, and a decreased prevalence of gastrointestinal involvement.

Key words: Behçet's disease, human leucocyte antigens, genetics, meta-analysis.

Introduction

Behçet's disease (BD) is a rare chronic, inflammatory, multisystem disorder predominantly affecting populations of Asian, Middle Eastern and Mediterranean ancestry. With the exception of oral aphthosis, BD is characterized by considerable phenotypic variation, comprising a myriad of manifestations, e.g. recurrent genital ulcers and skin, joint, eye, vascular and/or CNS involvement. Over the last 30 years, a substantial body of knowledge has accumulated supporting a strong genetic underpinning in BD of the MHC-related allele *HLA-B5*, which was later more specifically linked to its predominant suballele *HLA-B51* [1, 2]. *HLA-B51* or *HLA-B5* (henceforth denoted *HLA-B51/B5*) is carried by one- to two-thirds of patients and increases the risk of BD development by a factor of about 6 [3].

The protean nature of clinical BD manifestations raised the question of whether *HLA-B51/B5* also has a modulatory effect on disease expression. Study results suggested that *HLA-B51/B5*-positive and negative BD

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patients differed in that the former more frequently developed CNS [4] or eye involvement [2, 5] and the latter more commonly thrombophlebitis [6]. In addition, it was suggested that patients harbouring the *HLA-B51/B5* allele have more unfavourable BD courses, characterized by poorer outcomes of ocular [4, 7, 8] or neurological involvement [4]. However, these observations have not been reported consistently [9, 10] and the discrepancies may have been exacerbated by studies with small sample sizes. In light of the potential implications of this matter in clinical practice and for the understanding of BD pathogenesis, a meta-analysis of observational studies appeared suitable to elucidate the relationships between the *HLA-B51/B5* genetic background and clinical BD phenotype. We report the results of a systematic literature review and meta-analyses of observational case studies in an attempt to clarify potential relationships between *HLA-B51/B5* and BD-related phenotypic manifestations.

Methods

Data sources and searches

We searched the literature for BD case studies using the PubMed MEDLINE and Embase databases to identify publications relevant to the purpose of this study, without any language restriction. The search period was January 1973 through September 2008. Various combinations of the following medical subject headings and keywords were used in searching: Behçet's disease, Behçet's syndrome, HLAs, *HLA-B5* and *HLA-B51*. Reference lists from the retrieved publications and references identified in a previous systematic literature review on the *HLA-B51/B5* association with BD [3] were also reviewed and additional Google Internet searches were performed.

Study selection and data extraction

Eligible publications were those providing information on the distribution of one or more phenotypic BD characteristics, defined as demographic characteristics (age, sex) and generic or specific organ or system manifestations, according to *HLA-B51/B5* status of BD cases. From each eligible publication, two readers (C.M., M.C.) independently gathered data using a structured data collection form. In addition to the distributions of cases with and without the relevant clinical variable(s) according to *HLA-B51/B5* status, the form included information on author and study area, publication year, type and language, BD classification criteria used, screened allele and genotyping technique. Between-reader inconsistencies in the collected information were resolved by discussion and re-analysis of the original data and, when necessary, third-party adjudication (A.M.) until a consensus was reached. Any publication reporting on less than 10 BD patients was excluded a priori.

When several reports were published by the same research centres, we assessed potential overlap of patient data to avoid inclusion of publications analysing the same or overlapping subjects. Unless this information was explicitly given in multiple publications from the same institution, the authors were contacted personally or by e-mail for clarification. For studies with overlapping subjects reporting on the same genotype–phenotype outcomes, we used the data from the publication reporting on the highest number of individuals. Selected genotype–phenotype data from smaller overlapping publications were also taken into consideration when they had not been given in the larger publication.

Subsequently, all clinical variables for which relevant information was identified were categorized into homogeneous groups. The findings reported on the features orchitis and epididymitis were combined under the term orchiepididymitis.

Data synthesis and analysis

A meta-analysis was generated for each clinical variable for which five or more studies had been identified with relevant information of its distribution as a function of *HLA-B51/B5* status. For each meta-analysis, we calculated the relative risk (RR) and the 95% CIs for individual studies and estimated the pooled RR (95% CI) using fixed- and random-effects meta-analysis models [11]. Although both models yielded similar estimates in most instances, only random-effects results are presented herein because between-study heterogeneity was identified in some meta-analyses. Heterogeneity across studies was evaluated with the DerSimonian–Laird χ^2-based *Q*-statistic [12]. We also computed the I^2-statistic, which is the percentage of total variation of RR estimates attributable to between-study heterogeneity, rather than sampling error [13, 14]. To assess the possibility of publication bias, we used the Egger test [15], the Begg test (adjusted rank-correlation test) [16] and contour-enhanced funnel plots [17]; the latter were assessed visually for symmetry and location of study values relative to contours determined by significance levels of 0.1, 0.05 and 0.01.

The robustness of the observed results was evaluated by a pre-defined sensitivity analysis in which only studies with 50 or more BD subjects were included in the meta-analyses. Following the same algorithm as that applied to the primary analyses, meta-analyses were generated exclusively for clinical variables with at least five informative studies. To further explore the impact of specific study-level characteristics on the RR for BD characteristics by *HLA-B51/B5* carriage, we undertook univariate random-effects meta-regression, using male sex, genital ulcers, eye and skin involvement as dependent variables and geographic area (stratified by Asia, Middle East/North Africa and Europe), *HLA-B51 vs HLA-B5* genotype, serological *vs* molecular HLA testing, publication language (English *vs* other), publication type (peer-reviewed article *vs* publication in books/conference proceedings) and year of publication as explanatory variables.

Within each of the meta-analysis data sets, we also calculated the pooled prevalence, expressed as percentages (95% CI), of the corresponding clinical variable and the pooled prevalences of *HLA-B51/B5*. In addition to the calculations based on the entire data sets, prevalences of

clinical variables were computed within the *HLA-B51/B5*-positive and negative subgroups. These calculations also used random-effects meta-analysis techniques, as previously described [18].

All statistical analyses were conducted with SAS (version 9.1; Cary, NC, USA). Statistical tests were two-tailed and statistical significance was defined as $P < 0.05$, except for the tests for publication bias, whose significance level was set at a conservative value of $P < 0.10$.

Results

Search results and description of studies

Fig. 1 summarizes the study selection process. Among 859 titles, abstracts or full reports identified and reviewed, 769 did not satisfy the pre-stated inclusion criteria. Among the 90 potentially relevant articles, 13 were excluded [19–31] because they contained fully overlapping information with one or several other publications. Five other studies were excluded because they informed on outcome variables, i.e. oral ulcers [32–34], arterial involvement [35] and/or age [34, 36], which did not qualify for performing a meta-analysis (see below).

Finally, 72 articles were retained that contributed data to one or more clinical BD-characteristic genotype relationships [2, 5–10, 37–101]. From 14 publications [10, 37, 39, 41, 52, 69, 71, 84, 86, 96–98, 100, 101], only selected information on all available clinical BD phenotype–genotype associations was used because these publications had overlapping patient data with other publications. Two of the 72 publications referred to paediatric series [67, 93]. For one study, whose reported BD cases included several related subjects, only the data on unrelated individuals were used [59]. Three reports included two geographical populations [47, 86, 97], which were considered separately; for one of them [97], data on one geographical population were not used because of an overlap with another publication. Thus the 72 publications retained concerned 74 patient populations.

Detailed characteristics of the 74 study populations used for the meta-analyses are shown in Table 1. Thirty-five study populations assessed the genotype–phenotype associations for *HLA-B5* and 34 study populations for *HLA-B51*. In addition, four study populations provided information on both *HLA-B5* and *HLA-B51* [39, 44, 46, 57]; we used *HLA-B5* data from three publications [44, 46, 57] and *HLA-B51* data from the remaining study [39], because this approach maximized the numbers of informative cases. The results of another study, in which the *HLA-B5101* suballele was genotyped, were assigned to the subcategory of studies with genotyped *HLA-B51* [68]. Classification criteria used were the International Study Group (ISG) criteria [102] (27 study populations), 1974/1987 revised Japanese BD research committee (JBDRC) criteria [103, 104] (21 study populations), other criteria [75, 105–110] (18 study populations), or were study-specific or unstated (8 study populations). Most of the analysed publications were full-length reports in peer-reviewed journals (61 study populations) and were written in English (59 study populations). Geographical

Fig. 1 Flow diagram of the study selection process.

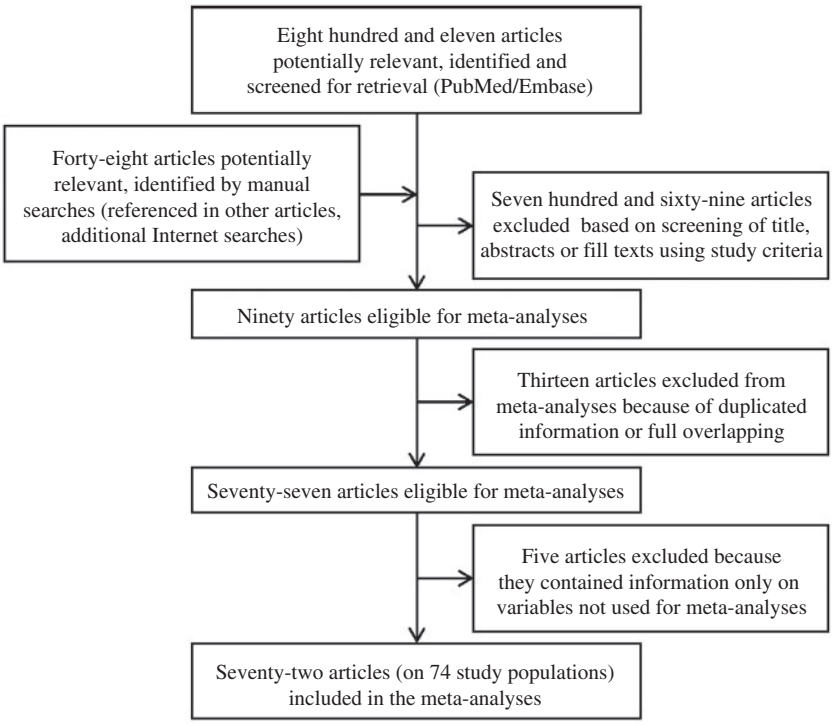


Table 1 Characteristics of 74 observational study populations (from 72 publications) used for meta-analyses of clinical feature—*HLA-B51/B5* genotype relationships

Study	Reference type	Country	Area	Sample size	Criteria[a]	Allele tested	Manifestations analysed
Adorno *et al*. [37]	PRJ	Italy	Europe	27	JBDRC	*B5*	Eye, GI, G-Ulc, joint, neuro, orch, skin, vasc
Alballa *et al*. [38]	CP	Saudi Arabia	M. East	84	Mason and Barnes	*B51*	Eye, neuro, sex, vasc
Al-Dalaan *et al*. [39]	PRJ	Saudi Arabia	M. East	32	Mason and Barnes	*B51*	Chest, GI, G-Ulc, joint, skin
Alekberova *et al*. [40]	PRJ	Russia	Europe	151	ISG	*B51*	Sex, TPitis
Alekberova *et al*. [41]	PRJ	Russia	Europe	19	ISG	*B5*	GI, G-Ulc, joint, PT, skin
Alpsoy *et al*. [42]	PRJ	Turkey	M. East	71	ISG	*B51*	Eye, GI, G-Ulc, joint, neuro, PT, skin, vasc
Ambresin *et al*. [43]	PRJ	Switzerland	Europe	28	JBDRC	*B51*	Eye
Anti *et al*. [44]	CP	Italy	Europe	20	Mason and Barnes	*B5*	Eye, GI, G-Ulc, joint, neuro, sex, skin, vasc
Aramaki *et al*. [45]	PRJ	Japan	Asia	150	ISG	*B51*	Neuro, sex
Assaad-Khalil *et al*. [46]	CP	Egypt	N. Africa	168	ISG	*B5*	Neuro
Azizlerli *et al*. [6]	PRJ	Turkey	M. East	235	O'Duffy	*B5*	EN, eye, G-Ulc, joint, PF, sex, TPitis
Bhakta *et al*. [47]	CP	Turkey	M. East	156	ISG	*B5*	Eye, sex
Bhakta *et al*. [47]	CP	UK	Europe	87	ISG	*B5*	Eye, sex
Boura *et al*. [48]	PRJ	Greece	Europe	31	ISG	*B51*	Eye, G-Ulc, neuro, PT, sex, skin
Castillo Palma *et al*. [49]	PRJ	Spain	Europe	67	O'Duffy	*B51*	Eye, GI, joint, neuro, orch, sex, skin, TPitis
Chajek-Shaul *et al*. [50]	PRJ	Israel	M. East	42	JBDRC	*B51*	Eye, G-Ulc, joint, neuro, orch, sex, skin, TPitis, vasc
Chang *et al*. [51]	PRJ	Korea	Asia	61	JBDRC	*B51*	EN, eye, GI, G-Ulc, joint, neuro, sex
Choukri *et al*. [52]	PRJ	Morocco	N. Africa	86	ISG	*B51*	Sex
Choukri *et al*. [53]	PRJ	Morocco	N. Africa	86	ISG	*B51*	Eye, joint, neuro, PT, TPitis
Chung *et al*. [54]	PRJ	China	Asia	51	JBDRC	*B51*	Eye, sex
Ermakova *et al*. [22]	CP	Russia	Europe	30	ISG	*B5*	Eye
Fernandez Miranda *et al*. [56]	PRJ	Spain	Europe	16	Multiple sets	*B5*	Sex
Freire *et al*. [57]	CP	Portugal	Europe	17	ISG	*B5*	Eye, G-Ulc, joint, neuro, sex, vasc
Gemignani *et al*. [58]	PRJ	Italy	Europe	20	Mason and Barnes	*B51*	EN, eye, G-Ulc, joint, neuro, orch, PT, sex, skin, TPitis
Gonzalez *et al*. [59]	PRJ	Spain	Europe	17	Multiple sets	*B5*	EN, eye, G-Ulc, joint, PT, PF, sex, skin
Gül *et al*. [9]	PRJ	Turkey	M. East	148	ISG	*B51*	EN, eye, G-Ulc, joint, neuro, PT, PF, skin, TPitis
Hamza *et al*. [60]	PRJ	Tunisia	N. Africa	135	Multiple sets	*B5*	Eye
Hong [61]	CP	Korea	Asia	12	JBDRC	*B51*	Eye, G-Ulc, joint, neuro, skin, vasc
Houman *et al*. [62]	PRJ	Tunisia	N. Africa	111	ISG	*B51*	Eye, neuro, TPitis
Inaba *et al*. [63]	CP	Japan	Asia	83	JBDRC	*B51*	Neuro
Jung *et al*. [64]	PRJ	UK	Europe	10	Not reported	*B5*	Eye, GI, G-Ulc, joint, neuro, sex, skin, TPitis
Kaya *et al*. [65]	PRJ	Turkey	M. East	85	ISG	*B51*	TPitis
Kilmartin *et al*. [66]	PRJ	Ireland	Europe	24	ISG	*B51*	Eye, sex
Kim *et al*. [7]	PRJ	Korea	Asia	24	JBDRC	*B51*	Eye, G-Ulc, joint, neuro, skin, vasc
Kone-Paut *et al*. [67]	PRJ	France	Europe	11	Multiple sets	*B5*	Eye, GI, G-Ulc, joint, neuro, orch, sex, skin, TPitis
Koumantaki *et al*. [68]	PRJ	Greece	Europe	62	ISG	*B5101*	EN, eye, sex
Krause *et al*. [69]	PRJ	Israel	M. East	55	ISG	*B5*	Chest, EN, eye, GI, G-Ulc, joint, neuro, skin, TPitis
Krause *et al*. [70]	PRJ	Israel	M. East	37	ISG	*B5*	PT

(continued)

Table 1 Continued

Study	Reference type	Country	Area	Sample size	Criteria[a]	Allele tested	Manifestations analysed
Krause *et al*. [71]	PRJ	Israel	M. East	24	ISG	*B5*	Sex
Krause *et al*. [72]	PRJ	Germany	Europe	136	ISG	*B51*	Eye
Kremer *et al*. [73]	PRJ	France	Europe	11	ISG	*B5*	EN, eye, GI, G-Ulc, neuro, sex, PT, PF, vasc
Lee *et al*. [74]	PRJ	Korea	Asia	52	Multiple sets	*B5*	Eye, joint, neuro
Lehner *et al*. [75]	PRJ	UK	Europe	65	Curth	*B5*	Eye
Mansoori *et al*. [76]	CP	Iran	M. East	244	JBDRC	*B5*	PT
Mitrovic *et al*. [77]	PRJ	Serbia	Europe	12	Not reported	*B5*	Eye, G-Ulc, joint, neuro, sex, skin, vasc
Mizuki *et al*. [78]	PRJ	Japan	Asia	95	JBDRC	*B51*	Eye
Muftuoglu *et al*. [10]	PRJ	Turkey	M. East	119	O'Duffy	*B5*	EN, joint, TPitis
Mustafa and Hadid [79]	PRJ	Jordan	M. East	124	Multiple sets	*B5*	Eye, G-Ulc, skin
Najim *et al*. [80]	PRJ	Iraq	M. East	41	ISG	*B51*	Sex
Ning *et al*. [81]	PRJ	China	Asia	27	Not reported	*B51*	Sex
Ning-Sheng *et al*. [82]	PRJ	China	Asia	28	ISG	*B51*	EN, GI, G-Ulc, PF, sex, TPitis
Nishiyama *et al*. [84]	PRJ	Japan	Asia	68	JBDRC	*B51*	GI, G-Ulc, joint, neuro, orch, PT, skin, vasc
Nishiyama *et al*. [83]	PRJ	Japan	Asia	2960	JBDRC	*B51*	Eye, sex
Ohno *et al*. [2]	PRJ	Japan	Asia	184	JBDRC	*B5*	Eye, sex
Okinami *et al*. [85]	PRJ	Japan	Asia	45	JBDRC	*B5*	Eye
Okuyama *et al*. [86]	CP	Japan	Asia	19	JBDRC	*B51*	PT
Okuyama *et al*. [86]	CP	Italy	Europe	10	JBDRC	*B51*	EN, eye, GI, G-Ulc, joint, PT, sex
Pipitone *et al*. [87]	PRJ	Italy	Europe	112	ISG	*B51*	Sex
Pivetti Pezzi *et al*. [88]	PRJ	Italy	Europe	51	JBDRC	*B5*	Sex
Sekido *et al*. [89]	PRJ	Japan	Asia	32	JBDRC	*B5*	Eye
Si *et al*. [90]	PRJ	China	Asia	40	Not reported	*B5*	Eye
Soylu *et al*. [8]	PRJ	Turkey	M. East	65	Not reported	*B5*	Eye
Takano *et al*. [91]	PRJ	Japan	Asia	54	JBDRC	*B5*	Sex
Terayama *et al*. [92]	PRJ	Japan	Asia	41	JBDRC	*B51*	Eye, sex
Uziel *et al*. [93]	PRJ	Israel	M. East	26	Study-specific	*B5*	Chest, EN, eye, GI, G-Ulc, joint, neuro, PT, sex, skin, TPitis
Verity *et al*. [5]	PRJ	Jordan/Palestine	M. East	101	ISG	*B51*	Eye, sex
Wang *et al*. [94]	PRJ	China	Asia	27	Not reported	*B51*	Eye
Wechsler *et al*. [95]	PRJ	France	Europe	50	JBDRC	*B5*	Chest, eye, GI, G-Ulc, joint, neuro, sex, skin, TPitis
Yazici *et al*. [96]	PRJ	Turkey	M. East	19	O'Duffy	*B5*	Neuro
Yazici *et al*. [97]	PRJ	UK	Europe	14	O'Duffy	*B51*	G-Ulc, joint, skin, TPitis
Yazici *et al*. [98]	PRJ	Turkey	M. East	49	O'Duffy	*B5*	Chest, G-Ulc, PT, skin
Yurdakul *et al*. [99]	PRJ	Turkey	M. East	19	Study-specific	*B5*	EN, G-Ulc, joint, PF, PT, sex
Zouboulis *et al*. [100]	CP	Germany	Europe	40	ISG	*B5*	Chest, EN, GI, G-Ulc, joint, neuro, PT
Zouboulis *et al*. [101]	PRJ	Germany	Europe	64	Davatchi	*B5*	Sex, skin, TPitis, vasc

[a]References for classification criteria: Curth [108], Davatchi *et al*. [109], ISG [102], JBDRC [103, 104], Mason and Barnes [105] and O'Duffy [110]. CP: conference proceedings; EN: erythema nodosum; GI: gastrointestinal; G-Ulc: genital ulcers; M. East: Middle East; neuro: neurological; N. Africa: North Africa; orch: orchiepididymitis; PF: pseudofolliculitis; PRJ: peer-reviewed journal; PT: pathergy test; TPitis: thrombophlebitis; vasc: vascular.

distribution of the 74 study populations was Middle Eastern/North African countries 26, Asian nations 20 and European countries 28.

Description of selected clinical characteristics

Relevant information on the association with *HLA-B51/B5* could be extracted from five or more study populations for the following 14 phenotypic characteristics: male sex (39 populations), genital ulcers (30 populations), eye involvement (47 populations), skin involvement (24 populations), erythema nodosum (14 populations), pseudofolliculitis (6 populations), pathergy test (17 populations), joint involvement (29 populations), gastrointestinal involvement (17 populations), neurological involvement (29 populations), orchiepididymitis (5 populations), thrombophlebitis (18 populations), vascular involvement (12 populations) and chest involvement (6 populations). For each of these phenotypic characteristics, a list of the original parameter designations applied in the individual publications can be provided upon request.

In contrast, for the phenotypic variables—arterial disease, heart involvement, kidney involvement, myositis and audiovestibular involvement—five or fewer informative study populations were identified; hence these outcomes were not used for meta-analyses. For the outcome age (at disease onset, diagnosis or time of study), no meta-analysis was undertaken, due to insufficient data reported on variance, which precluded quantitative analyses. Also, no meta-analysis was generated for the variable oral ulcers because this manifestation is virtually present in all BD patients and also a mandatory ISG criterion [102]. We therefore thought it unlikely that *HLA-B51/B5* influences the occurrence of oral ulcers, thereby rendering meta-analysis inappropriate.

Relationships between HLA-B51/B5 status and clinical characteristics

The number of subjects included in each of the 14 clinical phenotype–genotype relationship meta-analyses ranged from 143 to 5790. Table 2 provides the pooled RR for each given manifestation among *HLA-B51/B5*-positive BD subjects compared with those not carrying this allele. The forest plots of all the study-specific RR estimates and the summary-effect estimates for the outcomes eye involvement and male sex are shown in Fig. 2.

These meta-analyses indicated that *HLA-B51/B5* carriage predominates in men (RR 1.14, 95% CI 1.05, 1.23, $P = 0.001$), and increases the risk of genital ulcers (RR 1.07, 95% CI 1.01, 1.14, $P = 0.03$), eye involvement (RR 1.13, 95% CI 1.06, 1.21, $P < 0.0005$) and skin involvement (RR 1.10, 95% CI 1.03, 1.16, $P = 0.003$), and decreases risk of gastrointestinal involvement (RR 0.70, 95% CI 0.52, 0.94, $P = 0.02$). No statistically significant effects of *HLA-B51/B5* on the other analysed phenotypic features were observed.

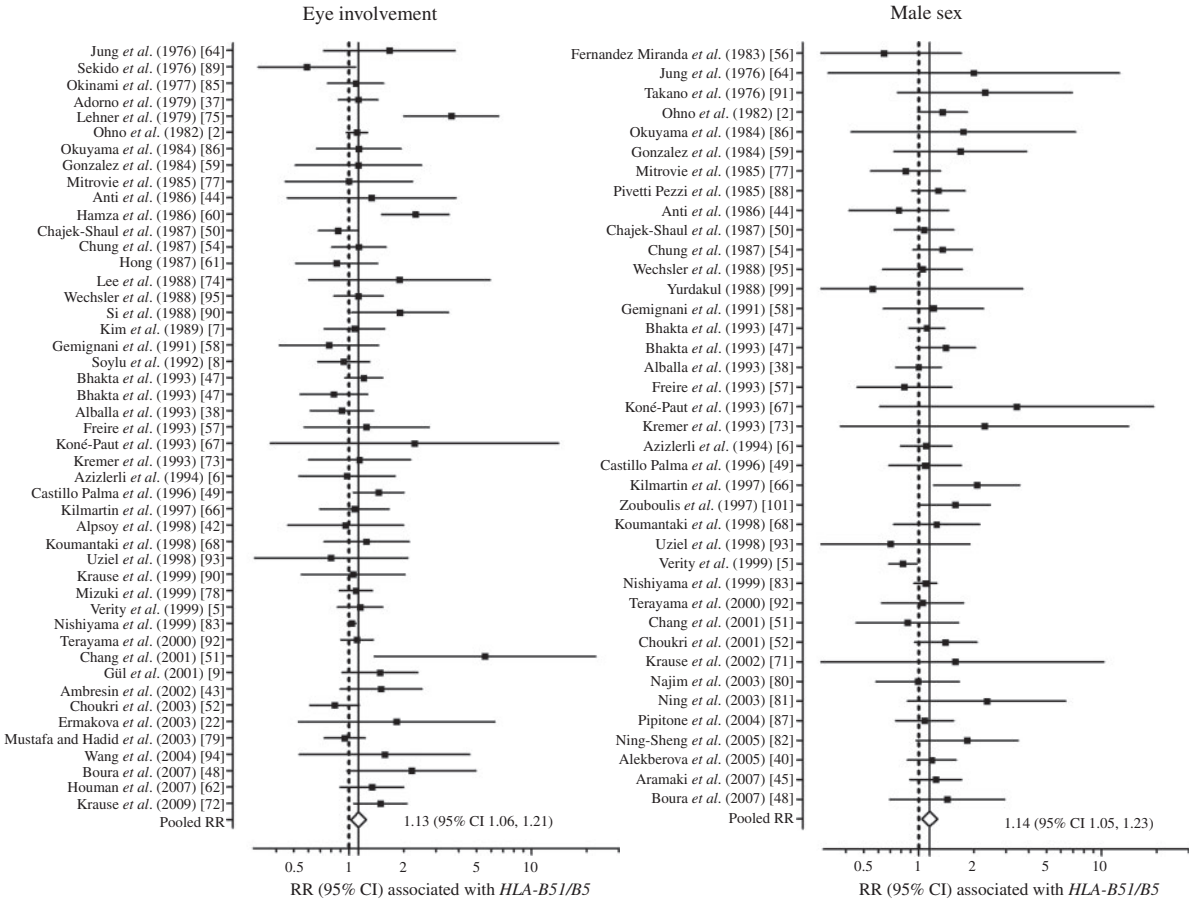
I^2-statistics indicated moderate heterogeneity in the analyses for thrombophlebitis ($I^2 = 56\%$) and low

Table 2 Summary statistics for each of the 14 clinical BD features' random-effects pooled prevalence and pooled estimate of association with *HLA-B51/B5*

Clinical variable[a]	Number of study populations	Number of subjects	Pooled prevalence (95% CI)	Effect size		Heterogeneity statistics		Publication bias	
				RR (95% CI)	*P*	*P* (Q-test)	I^2 (%)	*P* (Egger test)	*P* (Begg test)
Eye involvement	47	5790	63.5 (57.2, 69.3)	1.13 (1.06, 1.21)	<0.0005	0.004	38.9	0.01	0.13
Male sex	39	2720	58.9 (54.1, 63.4)	1.14 (1.05, 1.23)	0.001	0.20	15.6	0.02	0.49
Genital ulcers	30	1303	79.8 (74.0, 84.5)	1.07 (1.01, 1.14)	0.03	0.71	0	0.77	0.53
Neurological involvement	29	1526	17.0 (12.7, 22.3)	0.95 (0.71, 1.27)	0.72	0.14	22.2	0.69	0.72
Joint involvement	29	1384	54.4 (47.7, 69.0)	0.94 (0.86, 1.04)	0.23	0.78	0	0.95	0.57
Skin involvement	24	1013	76.8 (69.2, 82.9)	1.10 (1.03, 1.16)	0.003	0.47	0	0.84	0.59
Thrombophlebitis	18	1322	19.9 (15.3, 25.5)	1.17 (0.77, 1.76)	0.46	0.001	56.4	0.03	0.10
Positive pathergy test	17	913	54.1 (42.9, 64.9)	1.05 (0.94, 1.17)	0.36	0.38	6.7	0.88	1.0
Gastrointestinal involvement	17	606	23.8 (16.6, 32.9)	0.70 (0.52, 0.94)	0.02	0.36	7.7	0.49	0.62
Erythema nodosum	14	849	47.5 (38.6, 56.5)	1.11 (0.96, 1.29)	0.17	0.02	47.8	0.74	0.96
Vascular involvement	12	452	23.3 (17.1, 38.3)	1.00 (0.68, 1.47)	1.0	0.45	0	0.19	0.41
Pseudofolliculitis	6	458	68.7 (41.5, 87.2)	1.07 (0.93, 1.23)	0.34	0.41	1.5	0.99	0.57
Chest involvement	6	252	9.2 (5.1, 16.2)	1.55 (0.75, 3.20)	0.24	0.58	0	0.09	0.04
Orchiepididymitis	5	143	14.2 (4.2, 38.4)	1.13 (0.59, 2.15)	0.72	0.93	0	0.26	0.62

[a]Variables are ordered by decreasing number of individual study populations and subjects used for each of the 14 meta-analyses.

Fig. 2 Forest plots of the meta-analyses on the RR for eye involvement and male sex associated with *HLA-B51/B5* carriage in BD. Individual studies are arranged in chronological order of publication.



heterogeneity for eye involvement ($I^2 = 39\%$) and erythema nodosum ($I^2 = 48\%$); *Q*-statistics were significant for eye involvement ($P = 0.004$), thrombophlebitis ($P = 0.001$) and erythema nodosum ($P = 0.02$). For all other variables, between-study heterogeneity assessed by I^2 was low or absent and the *Q*-statistic results were not significant.

The search for publication bias according to Begg and Egger tests (Table 2) and the patterns of the contour-enhanced funnel plots (not shown) suggested that publication bias was present in the meta-analyses of eye involvement, male sex and erythema nodosum, which could indicate that the pooled RR for these characteristics is somewhat inflated.

Sensitivity analyses that removed all studies that included 50 or fewer subjects were performed for 10 variables with five or more informative studies. These analyses yielded very similar RR point estimates to those obtained using the whole data sets (see supplementary Table S1, available at *Rheumatology* Online). In addition, after reanalysis of the association with eye involvement or male sex after removal of one very large study reporting on both variables [83], the pooled RR point estimates for these two variables were unchanged (data not shown).

The results of meta-regression analyses suggested that some of the variation of study results for associations of eye involvement or male sex with *HLA-B51/B5* could be linked to study-level characteristics (Table 3). In particular, the RR values for eye manifestations and *HLA-B51/B5* were higher when classification systems other than the ISG or JBDRC criteria were used when studies were conducted in Europe or when they were not published in English. The RR for association of male sex and *HLA-B51/B5* was lower in studies conducted in the Middle East or North Africa (data not shown). None of the other BD features and study characteristics had significant associations in meta-regression analyses.

Frequency estimates of phenotypic characteristics and *HLA-B51/B5*

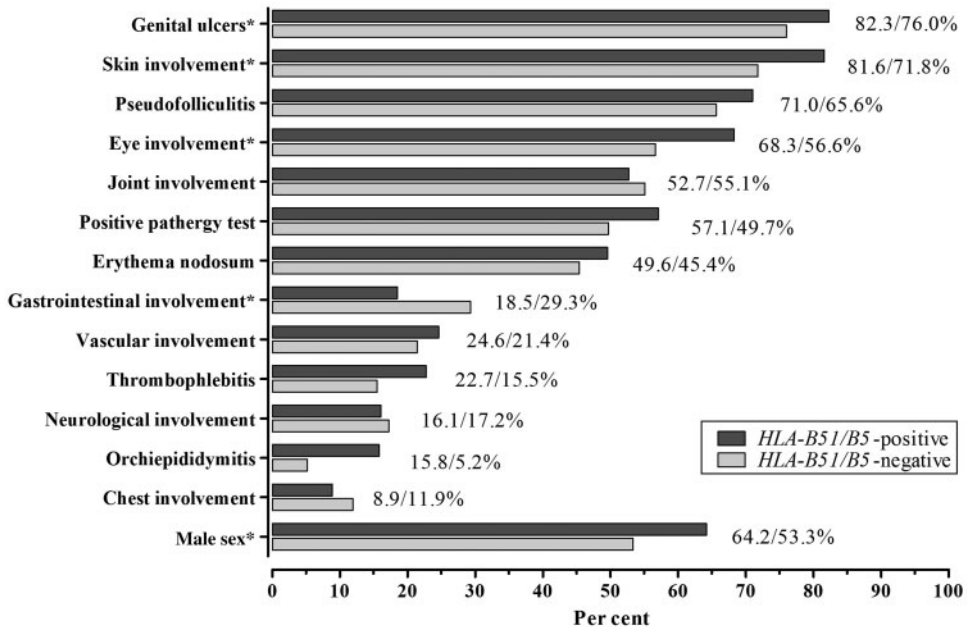
Based on the 14 meta-analysis data sets, we calculated pooled frequencies of the phenotypic BD characteristics and the pooled frequencies of *HLA-B51/B5* carriage.

TABLE 3 Meta-regression analyses assessing the effect of selected covariates on the pooled effect size of *HLA-B51/B5* carriage on the risk for BD-related characteristics

Covariate	Eye involvement		Male sex		Genital ulcers		Skin involvement	
	Number of study populations	P_{cov}	Number of study populations	P_{cov}	Number of study populations	P_{cov}	Number of study populations	P_{cov}
Peer-reviewed journal (yes/no)	39/8	0.40	33/6	0.49	25/5	0.98	22/2	0.71
Classification criteria (three categories)[a]	15/15/17	0.03	15/10/14	0.81	9/8/13	0.36	5/6/13	0.47
Geographic location (three categories)[b]	13/14/20	0.01	9/10/20	0.04	5/10/15	0.39	3/8/13	0.55
Allele genotypes (*HLA-B51/HLA-B5)*	23/24	0.52	19/20	0.63	13/17	0.48	11/13	0.56
Genotyping method (serological/molecular/NR)	25/6/16	0.80	18/5/16	0.06	14/4/12	0.24	12/2/10	0.79
Publication year	47	0.91	39	0.85	30	0.92	24	0.79
Publication language (English/other)	36/11	0.008	29/10	0.80	24/6	0.32	18/6	0.26

[a]ISG criteria; JBDRC criteria; other criteria or not stated. [b]Asia; Middle East/North Africa; Europe. NR: not reported; P_{cov}: *P*-value for covariate in meta-regression.

FIG. 3 Pooled frequencies of clinical BD features according to *HLA-B51/B5* status derived from data sets combining 5–47 patient populations. For each clinical variable, percentages are given for *HLA-B51/B5*-positive *vs HLA-B51/B5*-negative subjects. Calculations used random-effects meta-analysis techniques. Primary analyses identified variables marked with an asterisk as having statistically significant increased or decreased RR of occurrence according to *HLA-B51/B5* status.



The results of these analyses are shown in Table 2. Fig. 3 shows the pooled frequencies of the phenotypic characteristics stratified by *HLA-B51/B5* status. The estimated proportions of *HLA-B51/B5*-positive cases in these 14 population pools ranged from 49.8% (95% CI 30.9%, 68.7%) (for the pseudofolliculitis meta-analysis) to 63.8% (95% CI 45.7%, 78.7%) (for the chest involvement meta-analysis).

Discussion

Herein we reported the findings of 14 comprehensive meta-analyses, which pooled between 5 and 47 individual study populations, to estimate the effect of *HLA-B51/B5* on BD clinical features. The summary estimates support that *HLA-B51/B5* carriage is associated with significant 7–13% relative increases of the prevalence of genital ulcers, ocular or skin involvement, and a significant 30% relative reduction on the prevalence of gastrointestinal involvement. A significant link between *HLA-B51/B5* positivity and male sex was also found.

Current understanding is that both innate and adaptive immune responses are implicated in BD pathogenesis [111]. Neutrophils, the prototypic cells of the innate immune system, are key effectors of BD, as highlighted by skin hyperreactivity (pathergy reaction), neutrophil infiltrates seen in papulopustular skin lesions [112] and the demonstrated efficacy of the neutrophil function-inhibitor colchicine [113] on BD skin lesions and uveitis [114, 115]. Intervention of the adaptive immune system is supported by the association of BD with *HLA-B51/B5*, findings of an oligoclonal profile of the T-lymphocyte repertoire [116] and the efficacy of immunosuppressive therapy against some BD manifestations [117]. As is true for virtually all MHC–disease associations [111, 118], the mechanism by which *HLA-B51* predisposes to BD remains elusive. The most compelling theory is that *HLA-B51* presents autoantigens to T-suppressor lymphocytes and thereby activates the immune system.

The main finding of this study was that *HLA-B51/B5* had only a modest phenotype-fostering effect in BD. It implies that the clinical pictures of *HLA-B51/B5*-positive and negative BD are virtually indistinguishable, and that genotyping of this allele cannot accurately predict the occurrence of specific organ or system manifestations. That *HLA-B51/B5* was not significantly associated with the main markers of increased mortality, i.e. major vessel involvement [119, 120] or CNS disease [119, 121], indirectly suggests that this allele cannot serve as a mortality risk surrogate. In this study, the genetic effects were mainly assessed as generic organ or system involvements (e.g. eye involvement) and it cannot be excluded that *HLA-B51/B5* positivity drives a particular pattern of organ or system involvement (e.g. posterior uveitis). Thus the majority of computed RR only marginally deviated from the line of identity, making it unlikely that *HLA-B51/B5* has a numerically strong and clinically meaningful effect on a specific clinical manifestation. The observation that more variables were positively rather than negatively associated with *HLA-B51/B5* could still suggest that BD carriers of this allele have more extensive disease.

Notwithstanding, the slight but significant frequency increases observed for genital ulcers, skin involvement and eye involvement among *HLA-B51/B5* allele carriers merit consideration. These findings suggest that these manifestations, which form with oral ulcers the core symptoms of BD [102], have a shared pathogenetic pathway and favour the idea that *HLA-B51/B5* has a permissive effect on their development. When adhering to the paradigm that cutaneous and ocular manifestations are essentially neutrophil induced, these results add support to previous observations of a connection between *HLA-B51* positivity and neutrophil dysfunction. Although not uncontested [122], results of studies on mice and humans have suggested that *HLA-B51* plays a role in neutrophil activation [123] and chemotaxis [50, 124]. In contrast, the protective role of *HLA-B51/B5* on gastrointestinal disease is difficult to conceptualize. The hazy clinical line between gastrointestinal BD and other inflammatory bowel diseases, namely ulcerative colitis and Crohn's disease [4], for which no relationship with *HLA-B51/B5* exists [125], begs the question as to whether this finding mirrors some degree of diagnostic misclassification.

Another remarkable indication of this study is that *HLA-B51/B5* carriage was more common in male BD patients. Similar observations were made previously [31, 52, 66, 75], and they also agree with the findings of another meta-analysis that showed that the strength of the *HLA-B51/B5*–BD relationship was positively correlated with the proportion of male cases included in individual studies [3]. It could be advanced that the link between *HLA-B51/B5* and male sex is merely confounded by the previously reported evidence suggesting that male BD cases are more prone to eye involvement [66, 126–130]. However, the results of a study in which the *HLA-B51*–ocular disease relationship was stratified by sex suggested that the ocular disease-promoting effect of this allele is not restricted to males [54]. Moreover, as highlighted by the estimate that 59% were males in our corresponding meta-analysis data set, a male predominance in BD has been seen in many geographical areas [131] and could provide indirect support for *HLA-B51/B5* conferring enhanced BD risk to men.

Whether this sex-specific effect accounts for genetic or non-genetic epistasis is elusive. It was reported that testosterone levels correlated with markers of neutrophil activation in BD patients [132], and collectively these observations could indicate that male hormones act in concert with *HLA-B51/B5*, contributing to neutrophil dysfunction. It is also worth noting that, in our meta-regression analysis, the *HLA-B51/B5* relationship with male sex was only found in studies conducted in Asia and Europe, but not the Middle East or North Africa.

The meta-analysis data sets enabled computation of frequency estimates for BD manifestations within large case populations. These pooled estimates could reflect a truer picture than those observed in individual hospital series, which are vulnerable to selection bias. As it was advanced that there are geographic variations of BD clinical expression [131], these numbers need to be interpreted with the caveat in mind that they combined distinct international locations. BD cases harbouring *HLA-B51/B5* ranged between 50% and 72% across the 14 meta-analysis data sets, and the consistency of these estimates with previously established figures [3] supports the representativeness of our assembled data sets.

A potential shortcoming of our analyses is the possible between-study differences in the definitions used for

organ and system involvements. In addition, publication bias likely occurred in the meta-analyses for sex and eye involvement, and selective reporting of the outcomes in the primary cohorts cannot be ruled out. Thus the possibility that our findings were substantially flawed by these aspects is tempered by the, at best, small statistical between-study heterogeneity in most of the generated meta-analyses, and the results remained robust in sensitivity analyses restricted to the larger studies. In addition, meta-regression analyses suggested that several study characteristics possibly affected the strengths of association between *HLA-B51/B5* and eye involvement, which could raise concern about the magnitude of the estimated risk of eye involvement with allele carriage. Another potential drawback of our study is that, for clinical features that are either uncommon or with only small numbers of identified informative studies, statistical power may have been insufficient.

In conclusion, these quantitative syntheses of the *HLA-B51/B5* impact on clinical BD features provide evidence that *HLA-B51/B5* positivity has only modest BD phenotype-modifying effect and emphasize the potential interplay between this allele and neutrophil dysfunction. This study's findings may contribute to improving our understanding of the clinical continuum of BD presentations and their pathophysiologies.

Rheumatology key messages

- *HLA-B51/B5* is moderately associated with genital ulcers, eye and skin involvement in BD.
- *HLA-B51/B5* carriage is slightly higher in male BD.
- In BD, *HLA-B51/B5* may exert its effect via a neutrophilic pathway.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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