

Association of Symptomatic Acute Human Parvovirus B19 Infection with Human Leukocyte Antigen Class I and II Alleles

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To determine the effect of the major histocompatibility complex on the development of symptoms during acute human parvovirus B19 infection, we compared human leukocyte antigen (HLA) class I and II alleles in 36 patients with symptomatic acute B19 infection with those in >900 control subjects from northwestern England. The frequency of each of HLA-DRB1*01 ($P = .016$), DRB1*04 ($P = .007$), and DRB1*07 ($P < .0001$) alleles was significantly higher in parvovirus B19 patients than in control subjects. In the parvovirus group, 63.9% carried the rheumatoid arthritis-associated shared epitope sequence, compared with 45% of control subjects (odds ratio [OR], 2.2; 95% confidence interval [CI], 0.97–4.8; $P = .04$), and carriage was associated with fatigue during the acute phase (OR, 4.2; 95% CI, 0.8–23.9; $P = .047$). All symptomatic parvovirus-associated HLA-DRB1 molecules carry a neutrally charged glutamine at position 10 and a positively charged lysine at position 12 of the first hypervariable region. HLA-B49 was associated with parvovirus infection independently of HLA-DRB1*01, DRB1*04, and DRB1*07.

Human parvovirus B19, which was discovered in 1975 [1], has been associated with an extremely wide variety of clinical manifestations. However, apart from predispositions, such as shortened red blood cell survival and immunosuppression, the factors that determine whether an infected person develops symptoms remain unknown. Although P antigen, or globoside, is the cellular receptor for parvovirus B19 [2] and its distribution may reflect the possible spectrum of symptoms of B19 infection [3], the prevalence of patients with the “p” phenotype who lack this antigen (1 in 200,000) [4] is too low to be a major factor determining the presence or absence of symptoms in an infection that has a seroprevalence as high as 60%–70% of the general population.

The immune system has been implicated in the mediation of a number of clinical manifestations of parvovirus B19 infection,

including rash and arthralgia [5], fatigue [6], and glomerulonephritis [7], and autoantibody production is increasingly associated with B19 infection [8, 9]. Specific antiviral antibody production is thought to be the major defense against B19 virus, because normal human immunoglobulin frequently clears the virus from peripheral blood, resulting in clinical improvement in immunosuppressed persons [10, 11] and because specific antibody protects against infection both in vivo and in vitro. In addition, lymphoproliferative responses have recently been demonstrated against VP1/2 antigens in persons with past B19 infection [12]. The particular progression of these events in an individual may be mediated by the type of CD4⁺ T cell response [13, 14] that has been shown for other viruses [15, 16].

Therefore, we hypothesized that HLAs may have a bearing on whether patients with acute B19 infection develop symptoms. To address this question, we compared HLA class I and II alleles in 36 patients with symptomatic acute B19 infection with those in control subjects from the same region of England.

Subjects, Materials, and Methods

Patients with symptomatic acute parvovirus B19 infection. Thirty-six patients with acute parvovirus B19 infection were identified by detection of serum anti-B19 IgM in response to suggestive symptoms as part of routine clinical practice. No markers of acute infection with other agents were found on testing. All patients were white and from northwestern England except for 1 Italian woman (patient 8) and 1 Jewish woman (patient 17). Blood samples were obtained from all patients at the time of or shortly after the onset

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Informed consent was obtained from the parvovirus B19-infected patients. The human experimentation guidelines of the US Department of Health and Human Services and those of the authors' institutions were followed.

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Table 1. Demographic data, clinical symptoms at acute infection and follow-up, duration of follow-up, B19 markers, and autoantibodies for 36 patients from northwestern England with symptomatic parvovirus B19 infection.

Patient	Age at onset, years	Sex	Acute-phase data ^a				Duration, months	Follow-up data		
			Clinical symptom(s)	Serum B19 DNA	NS1 IgG	RF		ANA	Clinical symptom(s) ^b	Serum B19 DNA
1	26	M	Rash	+	-	-	-	4	Fatigue	+
3	37	F	Arthralgia, anemia	+	-	-	-	2	Arthralgia	+
4	38	M	Thrombocytopenia	+	-	+	-	14	Thrombocytopenia	-
5	9	M	TAC, hereditary spherocytosis	+	-	+	-	27	—	-
6	44	F	Arthralgia, fatigue	+	-	+	+	23	Arthralgia, fatigue	-
7	25	F	Rash, lymphadenopathy	+	-	-	-	24	Fatigue	-
8	34	F	Arthralgia, fatigue	+	-	+	+	26	Arthralgia, lymphadenopathy, CFS	-
9	35	F	Rash, arthralgia, fatigue	+	-	+	+	22	Fatigue	-
11	40	F	Rash, arthralgia, fatigue	+	-	-	-	7	Arthralgia, CFS	+
12	39	F	Rash, arthralgia, fatigue	+	-	-	-	33	—	-
13	39	F	Rash, arthralgia, fatigue	+	-	+	-	26	—	-
14	42	F	Rash, arthralgia	+	+	+	-	11	—	-
15	28	F	Arthralgia	+	-	-	-	26	—	-
16	39	F	Rash, arthralgia	+	-	-	-	2	—	+
17	47	F	Arthralgia, anemia	+	-	-	+	19	Arthralgia	+
18	36	F	Rash	+	-	-	-	26	—	-
19	52	F	Rash, arthralgia, fatigue	+	+	+	-	26	—	-
20	27	F	Arthralgia, fatigue	+	-	+	-	30	CFS	-
21	44	F	Rash, arthralgia	+	-	-	+	21	Arthralgia	-
22	46	F	Arthralgia, fatigue	+	-	-	+	25	Arthralgia, fatigue	+
23	16	M	Fatigue	+	+	-	-	26	—	-
24	39	F	Arthralgia	+	-	-	-	25	—	-
25	39	F	Arthralgia, fatigue, myalgia	+	-	-	-	15	—	+
26	35	F	Rash, fatigue	+	-	-	-	31	—	-
27	33	F	Fatigue	+	+	-	-	11	—	-
			Thrombocytopenia, myelodysplastic syndrome	-	-	-	-			
28	79	F	Arthralgia, fatigue	-	-	-	-	11	Thrombocytopenia	-
29	46	F	Arthralgia, fatigue	+	-	+	+	26	Arthralgia, fatigue	-
30	21	F	Rash, arthralgia, fatigue	+	-	-	+	27	—	-
32	46	M	Arthralgia, fatigue	+	-	+	-	30	Arthralgia, CFS	+
33	17	F	Rash, anemia	-	-	-	-	24	—	-
34	41	F	Arthralgia, fatigue	+	-	-	-	30	Arthralgia	-
35	41	F	Arthralgia	+	-	-	-	37	—	-
37	34	F	Rash, arthralgia, fatigue, myalgia	+	-	+	-	27	Fatigue	-
38	40	F	Rash, arthralgia, lymphadenopathy	+	-	-	-	26	—	-
39	40	F	IUD	+	+	+	-	25	—	+
40	32	F	IUD-R	+	+	-	-	26	—	-

NOTE. ANA, anti-nuclear antibody; CFS, chronic fatigue syndrome; IUD, intrauterine death without preceding maternal symptoms; IUD-R, intrauterine death with preceding maternal rash; NS1, nonstructural protein 1; RF, rheumatoid factor; TAC, transient aplastic crisis.

^a +, Positive; -, negative.

^b A (—) denotes absence of symptoms.

of new symptoms, and all patients were well and healthy by their own assessment prior to the onset of these symptoms. Follow-up and the sampling, processing, and storage of blood were as described elsewhere [17]. Clinical symptoms and levels of circulating cytokines for these patients have been reported elsewhere [6, 17].

Control subjects. Control subjects, who also were from northwestern England, were typed for HLA class I and II alleles: HLA-DRB1 ($n = 952$), HLA-DQB1 ($n = 931$), HLA-DP ($n = 966$), and HLA-B ($n = 965$). Analysis of the proportions of those possessing the shared epitope in case patients and control subjects was performed using data from a different set of 180 control subjects from northwestern England [18].

Detection of parvovirus B19 markers and autoantibodies. Parvovirus B19 markers (antibodies and DNA) and autoantibodies (rheumatoid factor and anti-nuclear antibody) were detected as described elsewhere [17].

HLA allele determination. HLA alleles were determined by hybridization of sequence-specific oligonucleotide probes to human genomic DNA extracted from whole blood.

Statistical analysis. The frequency distribution of alleles for HLA-DRB1, HLA-DQB1, HLA-DP, and HLA-B in the parvovirus B19-infected group initially was compared with that of control subjects by χ^2 tests for homogeneity. Each allele in the disease group that demonstrated significant differences to control subjects was then further examined by either χ^2 test or Fisher's exact analysis of 2×2 contingency tables. The strength of the association between parvovirus B19 infection and HLA alleles and phenotypes was estimated using odds ratios (ORs) and 95% confidence intervals (CIs). Where appropriate, P values were corrected for multiple comparisons, according to the procedure of Holm [19]. Multivariate logistic regression analysis was used to determine whether different HLA phenotypes were independently associated with par-

Table 2. HLA class I and II alleles in 36 patients from northwestern England with symptomatic acute parvovirus B19 infection.

Patient	HLA-DRB1	Shared-epitope alleles ^a	HLA-DQB1	HLA-DP	HLA-B
1	0403,0701		0201,0302	0404,0401	13,40
3	0101,15/16	+	0501,0602	0501,0901	07,35
4	0101,0401	++	0501,0301	0401,0402	40,44
5	0301,0407		0201,0301	0101,0301	07,08
6	0404,0407	+	03,03	02012,0301	40,44
7	0408,0701	+	0201,0301	0401,0402	1302,55
8	0701,0801		0201,0402	02012,0401	27,44
9	0101,1303	+	0501,0301	0501,0601	44,51
11	0401,0701	+	03,03	0101,1301	44,57
12	0404,0701	+	0201,0302	02012,11011	07,44
13	0401,13	+	0301,0603	0402,11011	44,44
14	0401,15/16	+	0302,0602	0401,0401	07,07
15	0301,0701		0201,0303	0401,3301	07,1402
16	0101,0401	++	0501,0301	0401,1401	44,44
17	0701,11		0201,0301	—	—
18	0701,13		0201,0604	0402,11011	44,4901
19	03,15/16		0201,0602	0401,0402	08,41
20	0701,04	+	0201,0302	02012,1901	08,1302
21	0301,07		0201,0303	0301,0401	08,27
22	0103,0401	+	0501,0301	0301,0401	07,3801
23	01,13/14	+	0501,0604	02012,0402	35,49
24	0301,0701		0201,0201	0101,0402	08,51
25	0701,15/16		0602,0201	0101,0401	15,47
26	0101,0101	++	0501,0501	0301,0402	4101,44
27	0101,0401	++	0501,0301	—	—
28	0101,0701	+	0501,0201	0101,02012	07,51
29	0101,0401	++	0501,0302	0401,0401	07,27
30	0405,15/16	+	0602,0302	02012,0401	07,4901
32	0404,0404	++	0302,0302	0401,0401	15,27
33	0401,0407	+	0301,0301	0301,0301	15,37
34	0101,0701	+	0501,0201	02012,0401	3503,44
35	0701,0701		0201,0201	0101,1701	44,44
37	0101,0101	++	0501,0501	02012,1001	35,5601
38	0301,13		0603,0201	02012,0401	08,3801
39	0701,0701		0201,0303	0301,0401	4901,51
40	0101,0301	+	0501,0201	0301,0401	07,08

^a +, One copy of shared epitopes; ++, two copies of shared epitopes.

vovirus infection. Forward stepwise logistic regression analysis was used to reveal the variables most strongly associated with disease. Analyses were done using the Number Cruncher Statistical System (version 6.0.4 for Windows; NCSS) or the PEPI Statistical Programs for Epidemiologists software package (version 2.0; USD) for epidemiologic analysis [20].

Results

Patients with symptomatic parvovirus B19 infection. Thirty-six patients with acute B19 infection (serum anti-B19 IgM positive) were studied both during the acute phase and again during convalescence. Details of clinical symptoms, B19 markers, autoantibodies, and duration of follow-up are shown in table 1. At follow-up, 4 of these patients fulfilled Centers for Disease Control and Prevention criteria for chronic fatigue syndrome, as described elsewhere [17] (table 1).

HLA-DRB1 allele associations in parvovirus patients versus control subjects. Allele frequencies of HLA-DRB1 in the case pa-

tient group are presented in table 2. Initial χ^2 analysis revealed that the frequency distribution of HLA-DRB1 alleles was significantly different between the parvovirus B19 group and control subjects (Pearson χ^2 , 26.7; *df*, 12; *P* = .008). Examination of adjusted residuals indicated that the frequencies of the HLA-DRB1*01, DRB1*04, and DRB1*07 alleles were significantly different among patients than among control subjects, and they made the largest contribution to the χ^2 value. Using 2×2 contingency tables, we found each of these alleles to be significantly more frequent among parvovirus B19 patients, compared with control subjects (table 3). Logistic regression analysis revealed that each of the HLA-DRB1*01, DRB1*04, and DRB1*07 phenotypes were independently associated with symptomatic acute parvovirus B19 infection. The strongest association was with HLA-DRB1*07 (*P* < .0001), although the associations with DRB1*01 (*P* = .016) and DRB1*04 (*P* = .007) were still significant. Overall, parvovirus-infected patients were significantly more likely to carry an HLA-DRB1*01, DRB1*04, or DRB1*07 allele than were control subjects. At least 1 of these alleles was found in 34 (94.4%) of 36 parvovirus-infected patients, compared

Table 3. HLA-DRB1 allele frequencies among symptomatic parvovirus-infected patients and control subjects from northwestern England.

HLA-DRB1	Case patients (<i>n</i> = 72)		Control subjects (<i>n</i> = 1904)	
	No.	Allele frequency	No.	Allele frequency
*01	15 ^a	0.208	242	0.127
*0101 or *0102	14	0.194	200	0.105
*0103	1	0.014	42	0.022
*03	7	0.097	314	0.165
*0301	6	0.083		
*04	20 ^b	0.278	340	0.179
*0401	9	0.125		
*0403	1	0.014		
*0404	4	0.056		
*0405	1	0.014		
*0407	3	0.042		
*0408	1	0.014		
*07	18 ^c	0.250	259	0.136
*0701	17	0.236		
*0801	1	0.014	36	0.019
*09	0	0	32	0.017
*10	0	0	6	0.003
*11	1	0.014	126	0.066
*12	0	0	37	0.019
*13	5	0.069	198	0.104
*14	0	0	46	0.024
*15	5	0.069	259	0.136
*16	0	0	9	0.005

NOTE. The overall frequency distribution was compared between patients and control subjects by using Pearson χ^2 (χ^2 [*df* 12] = 26.7; *P* = .008). Individual allele frequencies among patients and control subjects were compared by χ^2 analysis of 2×2 contingency tables.

^a Odds ratio (OR), 1.8; 95% confidence interval (CI), 0.96–3.3; *P* = .044.

^b OR, 1.8; 95% CI, 1.01–3.1; *P* = .032.

^c OR, 2.1; 95% CI, 1.2–3.8; *P* = .060.

with 574 (60.3%) of 952 control subjects (OR, 11.5; 95% CI, 2.7–69.6; $P < .0001$).

Many subtypes of HLA-DRB1*01 and DRB1*04 carry a conserved amino acid sequence (QKRAA, QRRAA, or RRRRAA) at position 70–74 in the third hypervariable region of the DR β chain. This so-called shared epitope is associated with both development and severity of rheumatoid arthritis [21]. In the symptomatic parvovirus group, 63.8% possessed the shared epitope, compared with 45% of control subjects (OR, 2.2; 95% CI, 0.97–4.8; $P = .04$) [18]. Furthermore, the carriage of 2 shared epitope alleles was 19.4% in the parvovirus group, compared with only 6.7% in the control subjects (OR, 3.4; 95% CI, 1.1–10.3; $P = .01$).

Although HLA-DRB1 alleles are in strong linkage disequilibrium with HLA-B, -DQB1 and -DP alleles, the association of symptomatic parvovirus B19 infection with DRB1*01, DRB1*04, and DRB1*07 alleles was independent of these other loci (data not shown).

HLA-DQB1, HLA-DP, and HLA-B associations in parvovirus patients versus control subjects. The overall frequency distribution of HLA-DQB1, -DP, and -B alleles in the parvovirus-infected group was not significantly different from that for control subjects. However, the frequency of both HLA-DQB1*06 (12.5% vs. 23.4%; OR, 0.47; 95% CI, 0.22–0.98; $P = .032$) and DP*0401 (29.2% vs. 43.0%; OR, 0.59; 95% CI, 0.31–0.95; $P = .05$) was lower in the symptomatic parvovirus B19-infected group than in control subjects. In addition, the frequency HLA-B49 was higher in the parvovirus group compared with control subjects (5.6% vs. 1.0%; OR, 6.49; 95% CI, 1.81–21.03; $P = .001$). The latter association was still significant ($P = .001$) in a multivariate regression model that included HLA-DRB1*01, DRB1*04, and DRB1*07 (data not shown).

HLA allele associations with particular symptoms or markers within the parvovirus group. We examined the parvovirus group for possible associations between the shared epitope and particular clinical manifestations, B19 markers, and autoantibodies at the acute infection stage and at follow-up. We found an association only in the case of fatigue. During acute B19 infection, only 4 (30.8%) of 13 shared epitope-negative patients had fatigue, compared with 15 (65.2%) of 23 shared epitope-positive patients (OR, 4.2; 95% CI, 0.8–23.9; $P = .047$). At follow-up, there was also an association, but it did not reach significance (OR, 2.13; 95% CI, 0.77–5.91; $P = .14$). Homozygous versus heterozygous carriage of the shared epitope did not alter the significance of this association (data not shown).

Sequence alignment of parvovirus-associated HLA-DRB1 alleles. Sequence alignment of HLA-DRB1*01, DRB1*04, and DRB1*07 alleles using the IMGT/HLA database (international Immunogenetics project; available online at <http://www.ebi.ac.uk/imgt/hla/index.html>) focused on the hypervariable regions of P1, P4, P6, P7, and P9 binding pockets [20] revealed a sequence and charge similarity within the first hypervariable region of DRB1*01, DRB1*04, and DRB1*07 that is different

from that of most non-associated molecules. Thus, all parvovirus-associated molecules carry a neutrally charged glutamine at position 10 and a positively charged lysine at position 12 (table 4).

Discussion

Parvovirus B19 infection is not uncommonly associated with clinical manifestations of a rheumatic nature or with diseases in which HLA molecules are known to be important in their pathogenesis [22]. For this reason, we hypothesized that particular HLA alleles may be associated with symptomatic as opposed to asymptomatic B19 infection. We found that HLA-DRB1*01, DRB1*04, and DRB1*07 were each independently associated with symptomatic parvovirus B19 infection. Many of the DRB1*01 and DRB1*04 subtypes encode the rheumatoid arthritis-associated “shared epitope” sequence [21]. However, DRB1*07 does not carry the shared epitope sequence, so this region is unlikely to fully explain the HLA-DR association with symptomatic parvovirus infection. Several other studies have examined the role of HLA-DR in the pathogenesis of parvovirus arthritis. The first of these examined a small number of patients ($n = 18$) and found a positive association between HLA-DR4 antigen and acute B19 arthritis [23], but this was not borne out in further studies [24–26]. Early studies were done using serologic typing, and results were reported in terms of antigen frequency. However, methods using oligonucleotide probes that determine specific HLA-DR alleles are much more accurate and provide information on the particular genotype of each patient. To our knowledge, previous to our study, the only other study to do HLA-DR molecular typing was by Gendi et al. [26], whose case ascertainment was identical to our own (i.e., positivity for serum anti-B19 IgM). They typed HLA-DRB1 alleles in 34 patients and 297 control subjects; however, they reported only on phenotype frequencies. In contrast to our study, Gendi et al. [26] found no associations between HLA-DR and parvovirus infection, although they did find that

Table 4. Protein sequence alignments encoded by different HLA-DRB1 alleles, showing the charge at the first hypervariable region, amino acids 9–13.

HLA-DRB1 allele	Amino acids at positions 9–13	Charge for each amino acid at positions 9–13	Net charge
*0101	WQLKF	n n n + n	+
*0301	EYSTS	- n n n n	-
*0401	EQVKH	- n n + +	+
*0701	WQGKY	n n n + n	+
*0801	EYSTS	- n n n n	-
*0901	KQDKF	+ n - + n	+
*1001	EEVKF	- - n + n	-
*1101	EYSTS	- n n n n	-
*1301	EYSTS	- n n n n	-
*1501	WQPKR	n n n + +	+
*1601	WQPKR	n n n + +	+

NOTE. n, neutral.

symptoms of the joints persisted for >1 week in all HLA-DR4-positive patients. A possible explanation is the ethnic background of parvovirus-infected patients. Although this was not documented in previous studies, the subjects in those studies were from southern England, which is known to have greater ethnic heterogeneity than does northwestern England, where our study was performed.

We have shown that HLA-B49 was associated with symptomatic parvovirus ($P = .001$). This was independent of the association with HLA-DRB1*01, DRB1*04, and DRB1*07. The role of the HLA-B locus in parvovirus B19 infection has previously been examined by Woolf et al. [24], who found no association when comparing patients with control subjects; however, these authors used serologic methods in only 26 patients and 318 control subjects. Persistent B19 arthritis has been linked previously with HLA-B27 [27], which is strongly associated with spondyloarthropathy, but we found no association with B27 in our study.

The association with DRB1*07 is particularly interesting, because this allele has been associated (usually with DQB1*02) with a variety of diseases and syndromes, including atopy [28, 29], antiphospholipid syndrome [30, 31], idiopathic nephrotic syndrome [32, 33], coeliac disease [34], and immotile cilia syndrome [35]. Parvovirus B19 infection has been associated with production of antiphospholipid antibodies and systemic lupus erythematosus [8, 36, 37] and with nephrotic syndrome and proteinuria [38].

HLA-DRB1*01, DRB1*04, and DRB1*07 alleles encode a glutamine at position 10 and a lysine at position 12 of the first hypervariable region. The significance of this is not entirely clear, because these particular residues do not appear to contribute directly to contact of the binding groove with bound peptide [20, 39]. However they may influence the binding ability of adjacent residues, such as the tryptophan at position 9. Polymorphism at this position has been associated with development of dermatomyositis-specific Mi-2 autoantibodies [40] and susceptibility to demyelinating polyneuropathy in plasma cell dyscrasia [41]. Consistent with a role of the first hypervariable region in symptomatic parvovirus infection, we recently found that 4 of 5 persons with parvovirus meningoencephalitis had ≥ 1 allele of DRB1*01, DRB1*04, and DRB1*07, whereas the fifth patient had DRB1*15 (which also carries glutamine at position 10 [Q¹⁰] and lysine at position 12 [K¹²]).

In conclusion, we report that HLA class I and II alleles are associated with symptomatic acute parvovirus B19 infection and suggest that further work is required to confirm the significance of these alleles in symptomatic parvovirus B19 infection.

References

- Cossart YE, Field AM, Cant B, Widdow D. Parvovirus-like particles in human sera. *Lancet* **1975**;1:72–3.
- Brown KE, Anderson SM, Young NS. Erythrocyte P antigen: cellular receptor for B19 parvovirus. *Science* **1993**;262:114–7.
- Cooling LL, Koerner TA, Naides SJ. Multiple glycosphingolipids determine the tissue tropism of parvovirus B19. *J Infect Dis* **1995**;172:1198–205.
- Brown KE, Hibbs JR, Gallinella G, et al. Resistance to parvovirus B19 infection due to lack of virus receptor (erythrocyte P antigen). *N Engl J Med* **1994**;330:1192–6.
- Anderson MJ, Higgins PG, Davis LR, et al. Experimental parvoviral infection in humans. *J Infect Dis* **1985**;152:257–65.
- Kerr JR, Barah F, Matthey DL, et al. Serum tumour necrosis factor- α (TNF- α) and interferon- γ (IFN- γ) are detectable during acute and convalescent parvovirus B19 infection and are associated with prolonged and chronic fatigue. *J Gen Virol* **2001**;82:3011–9.
- Takeda S, Takaeda C, Takazakura E, Haratake J. Renal involvement induced by human parvovirus B19. *Nephron* **2001**;89:280–5.
- Loizou S, Cazabon JK, Walport MJ, Tait D, So AK. Similarities of specificity and cofactor dependence in serum antiphospholipid antibodies from patients with human parvovirus B19 infection and from those with systemic lupus erythematosus. *Arthritis Rheum* **1997**;40:103–8.
- Lunardi C, Tiso M, Borgato L, et al. Chronic parvovirus B19 infection induces the production of anti-virus antibodies with autoantigen binding properties. *Eur J Immunol* **1998**;28:936–48.
- Kurtzman GJ, Frickhofen NK, Kimball J, Jenkins DW, Niehuis AW, Young NS. Pure red cell aplasia of 10 years duration due to persistent parvovirus infection and its cure with immunoglobulin therapy. *N Engl J Med* **1989**;321:519–23.
- Schwarz TF, Roggendorf B, Hottentrager B, Modrow S, Deinhardt F, Middeldorp J. Immunoglobulins in the prophylaxis of parvovirus B19 infection. *J Infect Dis* **1990**;162:1214.
- Von Poblitzki A, Gerdes C, Reischl U, Wolf H, Modrow S. Lymphoproliferative responses after infection with human parvovirus B19. *J Virol* **1996**;70:7327–30.
- Franssila R, Hokynar K, Hedman K. T helper cell-mediated in vitro responses of recently and remotely infected subjects to a recombinant vaccine for human parvovirus B19. *J Infect Dis* **2001**;183:805–9.
- Wagner A, Goronzy J, Matteson E, Weyand C. Systemic monocyte and T cell activation in a patient with human parvovirus B19 infection. *Mayo Clin Proc* **1995**;70:261–5.
- Goodbourn S, Didecock L, Randall RE. Interferons: cell signalling, immune modulation, antiviral response and virus countermeasures. *J Gen Virol* **2000**;81:2341–64.
- Hunter CA, Reiner SL. Cytokines and T cells in host defence. *Curr Opin Immunol* **2000**;12:413–8.
- Kerr JR, Bracewell J, Laing I, et al. Chronic fatigue syndrome (CFS) and arthralgia following parvovirus B19 infection. *J Rheumatol* **2002**;29:595–602.
- Matthey DL, Dawes PT, Bonzalez-Gay MA, et al. HLA-DRB1 alleles encoding an aspartic acid at position 70 protect against development of rheumatoid arthritis. *J Rheumatol* **2001**;28:232–9.
- Holm S. A simple sequentially rejective multiple test procedure. *Scand J Statistics* **1979**;6:65–70.
- Stern LJ, Brown JH, Jardetszky TS, et al. Crystal structure of the human class II MHC protein HLA-DR1 complexed with an influenza virus peptide. *Nature* **1994**;368:215–21.
- Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis: an approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* **1987**;30:1205–13.
- Kerr JR. The pathogenesis of human parvovirus B19 in rheumatic disease. *Ann Rheum Dis* **2000**;59:672–83.
- Klouda PT, Corbin SA, Bradley BA, Cohen BJ, Woolf AD. HLA and acute arthritis following human parvovirus infection. *Tissue Antigens* **1986**;28:318–9.
- Woolf AD, Campion GV, Chishick A, et al. Clinical manifestations of human parvovirus B19 in adults. *Arch Intern Med* **1989**;149:1153–6.
- Dykman BAC, Breedveld FC, de Vries RRP. HLA antigens in human parvovirus arthropathy. *J Rheumatol* **1986**;13:1192–3.

26. Gendi NST, Gibson K, Wordsworth BP. Effect of HLA type and hypocomplementaemia on the expression of parvovirus arthritis: one year follow-up of an outbreak. *Ann Rheum Dis* **1996**;55:63–5.
27. Jawad ASM. Persistent arthritis after human parvovirus B19 infection. *Lancet* **1993**;341:494.
28. Cardaba B, Vilches C, Martin E, et al. DR7 and DQ2 are positively associated with immunoglobulin-E response to the main antigen of olive pollen (Ole e I) in allergic patients. *Hum Immunol* **1993**;38:293–9.
29. Cardaba B, De Pablo R, Vilches C, et al. Allergy to olive pollen: T cell response from olive allergic patients is restricted by DR7-DQ2 antigens. *Clin Exp Allergy* **1996**;26:316–22.
30. Mujic F, Cuadrado MJ, Lloyd M, Khamashta MA, Page G, Hughes GR. Primary antiphospholipid syndrome evolving into systemic lupus erythematosus. *J Rheumatol* **1995**;22:1589–92.
31. Granados J, Vargas-Alarcon G, Drenkard C, et al. Relationship of anticardiolipin antibodies and antiphospholipid syndrome to HLA-DR7 in Mexican patients with systemic lupus erythematosus (SLE). *Lupus* **1997**;6:57–62.
32. Clark AG, Vaughan RW, Stephens HA, Chantler C, Williams DG, Welsh KI. Genes encoding the beta-chains of HLA-DR7 and HLA-DQw2 define major susceptibility determinants for idiopathic nephrotic syndrome. *Clin Sci* **1990**;78:391–7.
33. Bouissou F, Meissner I, Konrad M, et al. Clinical implications from studies of HLA antigens in idiopathic nephrotic syndrome in children. *Clin Nephrol* **1995**;44:279–83.
34. Ahmed AR, Yunis JJ, Marcus-Bagley D, et al. Major histocompatibility complex susceptibility genes for dermatitis herpetiformis compared with those for gluten-sensitive enteropathy. *J Exp Med* **1993**;178:2067–75.
35. Bianchi E, Savasta S, Calligaro A, et al. HLA haplotype segregation and ultrastructural study in familial immotile-cilia syndrome. *Hum Genet* **1992**;89:270–4.
36. Trapani S, Ermini M, Falcini F. Human parvovirus B19 infection: its relationship with systemic lupus erythematosus. *Semin Arthritis Rheum* **1999**;28:319–25.
37. Narvaez-Garcia FJ, Domingo-Domenech E, Castro-Bohorquez FJ, et al. Lupus-like presentation of parvovirus B19 infection. *Am J Med* **2001**;111:573–5.
38. Komatsuda A, Ohtani H, Nimura T, et al. Endocapillary proliferative glomerulonephritis in a patient with parvovirus B19 infection. *Am J Kidney Dis* **2000**;36:851–4.
39. Brown JH, Jardetzky TS, Gorga JC, et al. Three-dimensional structure of the human class II histocompatibility antigen HLA-DR1. *Nature* **1993**;364:33–9.
40. Mierau R, Dick T, Bartz-Bazzanella P, Keller E, Albert ED, Genth E. Strong association of dermatomyositis-specific Mi-2 autoantibodies with a tryptophan at position 9 of the HLA-DR beta chain. *Arthritis Rheum* **1996**;39:868–76.
41. Vrethem M, Ernerudh J, Cruz M, et al. Susceptibility to demyelinating polyneuropathy in plasma cell dyscrasia may be influenced by amino acid position 9 of the HLA-DR beta chain. *J Neuroimmunol* **1993**;43:139–44.