Immunoglobulin allotype Gm(1,2;21) in ankylosing spondylitis with peripheral arthritis

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SUMMARY Frequencies of immunoglobulin G (Gm) allotypes were determined in 240 patients with ankylosing spondylitis (AS). The uncommon phenotype Gm(1,2;21) was increased in frequency in 55 patients with AS and peripheral arthritis (14.5% v 3.5% of healthy blood donors; $p<0.05$). In 16 patients with arthritis only of wrist/hand or ankle/forefoot, or both, the Gm(1,2;21) frequency was even higher (31.3%; $p<0.0005$). Patients with AS negative for the HLA antigen B27 ($n=28$) differed from the B27 positive patients ($n=205$) with regard to the frequency of the Gm(1,2,3;5,21) phenotype (39.3% v 9.3%; $p<0.0005$). These findings support the notion of genetic heterogeneity among patients with AS.

Key words: immunogenetics, relative risk, HLA-B27.

Since its original description^{1,2} the association of ankylosing spondylitis (AS) with the antigen HLA-B27 has been verified extensively.³ Searches for further genetic predisposing factors for AS, besides HLA-B27 and male sex, have been successful recently. An association of AS with a polymorphic HLA restriction fragment⁴ as well as with the ABO blood group non-secretor state⁵ has been published, but a report of a high incidence of MM blood group homozygosity in AS⁶ was not confirmed by others.⁷ Raised frequencies of certain Gm allotypes situated on the immunoglobulin G chains⁸ have been reported for several rheumatic diseases⁹⁻¹⁷ but not for AS.^{18,19}

In the present study we reinvestigated the question of Gm associations in a large group of patients with AS, looking at patients grouped according to the presence or absence of the HLA-B27 antigen and at patients with different disease manifestations, particularly those with peripheral arthritis.

Subjects and methods

PATIENTS AND CONTROLS

Two hundred and forty patients of the Rheumaklinik Aachen (220 men, 20 women) fulfilling the New York criteria for AS²⁰ were included in the study. Their clinical and radiological data were evaluated retrospectively by chart review. Patients with psor-

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Table 1 Features of joint involvement in 55 patients with ankylosing spondylitis and peripheral arthritis. Values are numbers (percentages) of patients

	Patients with peripheral arthritis	
	Exclusively distal (n=16)	Distal and proximal or exclusively proximal (n=39)
Shoulder	—	7 (18)
Acromioclavicular	—	4 (10)
Elbow	—	8 (20.5)
Wrist	6 (37.5)	8 (20.5)
Metacarpophalangeal	7 (44)*	7 (18)*
Proximal interphalangeal	3 (19)	4 (10)
Distal interphalangeal	1 (6)	—
Hip	—	11 (28)
Knee	—	21 (54)
Ankle	6 (37.5)	11 (28)
Forefoot	12 (75)*	8 (20.5)*
Monarthritis	2 (12.5)	10 (25.5)
Oligoarthritis (2-4 joints)	8 (50)	14 (36)
Polyarthritis	6 (37.5)	15 (38.5)
Symmetrical arthritis	8 (50)	19 (49)
Erosions	8 (50)	13 (33)

*Significant difference between the two groups of patients, $p<0.0005$.

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iasis or inflammatory bowel disease were excluded. At the time of the investigation the mean (SD) age of the patients was 48 (10) years (range 23–75) and the mean disease duration 17 (9) years (range 2–56). From those 145 patients whose family data were available, 23 (16%) had first degree relatives with AS; in 15 cases (10%) other rheumatic complaints in the families were noted, and two patients (1%) had a family history of psoriasis.

Anterior uveitis had been recorded in 58 patients (24%) during the course of disease. In 55 cases (23%) peripheral arthritis was noted. Patients were included in this group if tenderness and swelling or direct inflammatory radiological alterations of the joints, or both, were recorded for fingers, toes, wrist, ankle, knee, elbow, or shoulder. Arthritis of the hip joint was only counted if proved radiologically. In 16 patients (7%) only the most distal joints (wrist, metacarpophalangeal and interphalangeal joints, ankle, and forefoot) were affected. Table 1 characterises further the joint involvement of our 55 patients with peripheral arthritis. The patients with the distal type of peripheral arthritis significantly more often had arthritis of metacarpophalangeal and metatarsophalangeal joints than AS patients with other kinds of peripheral arthritis. In 13 patients (5%) both anterior uveitis and peripheral arthritis were recorded.

Rheumatoid factor was measured in 164 patients, usually by both latex tests and sheep red blood cell agglutination assays. In eight cases (5%) rheumatoid factor was positive at least with one of these assays.

Two hundred and thirty three patients were typed for HLA-B27; all but 28 (12%) were positive for this marker.

Two hundred and twenty eight healthy Caucasian blood donors were used as the control group for comparing Gm phenotype frequencies.

Gm TYPING

The immunoglobulin G heavy chain allotypic markers G1m(1), G1m(2), G1m(3), G3m(5), and G3m(21) were determined by a haemagglutination inhibition assay,²¹ modified as described previously.¹⁵ Typing reagents were purchased from Biotest (Frankfurt, FRG) and Fresenius (Oberursel, FRG). The phenotypes of all control subjects and of all but two patients could be explained by combinations of the three common haplotypes Gm^{1,2,1}, Gm^{1,2,21}, and Gm^{3,5}. Phenotypic frequencies of these three haplotypes as well as the homozygous/heterozygous state of each subject were calculated by assuming all individuals typing Gm(1,2;21) and Gm(1,2;5,21) to be heterozygous carrying the haplotype Gm^{1,21} on one chromosome.

STATISTICS

Frequencies of Gm phenotypes, haplotypes, and homo/heterozygosity status were compared in patients and control subjects as well as in various patient subgroups and healthy blood donors by contingency table tests with Yates's correction. *p* Values were corrected by multiplying by the number of variables tested. Corrected *p* (*p_c*) values below 0.05 were judged as significant. Relative risk values were estimated by calculating odds ratios as described by Woolf.²²

Results

Table 2 lists the percentages of Gm frequencies for patients with AS and healthy control subjects as well as for patient subgroups.

None of the tested Gm markers was significantly increased or reduced in frequency, as compared with the control group, when the patient group as a whole was examined. In the patient subgroup with peripheral arthritis, however, the frequency of the Gm(1,2;21) phenotype was raised (14.5% *v* 3.5%, relative risk 4.7, *p_c* <0.05). Moreover, the 16 patients whose peripheral joint involvement was confined to hands or feet, or both ('distal' type) showed an even higher association with this particular Gm phenotype (31.3%, relative risk 12.5, *p_c* <0.0005). In addition, in this patient subgroup a reduction in frequency (of borderline significance) of the Gm^{3,5} haplotype was found (relative risk 0.17).

HLA-B27 positive or negative patients with AS did not differ significantly in Gm frequencies from healthy blood donors. There was a difference between the B27 negative and B27 positive group with respect to the frequency of the Gm(1,2,3;5,21) phenotype, however (39.3% *v* 9.3%, *p_c* <0.0005).

For patients with anterior uveitis no Gm association was found. Likewise, grouping of the patients according to early and late disease onset did not show differences in Gm frequencies (data not shown). In the group of female patients the Gm(1,2;21) frequency was raised in comparison with controls, but this difference lost statistical significance after correction of *p* values.

Discussion

The lack of associations between Gm types and ankylosing spondylitis as a whole is in agreement with previous reports.^{18,19} A trend towards increased Gm(1,2;21) and reduced Gm^{3,5} frequencies is present, however, in our data (Table 2) as well as in the report of Gran *et al.*¹⁹ We show here that this trend is almost exclusively due to a subgroup of

Table 2 Phenotypic Gm frequencies (percentages) in patients with AS, patient subgroups, and healthy controls

	Total group with AS (n=240)	AS plus peripheral arthritis (n=55)	AS plus peripheral arthritis, distal* (n=16)	AS plus anterior uveitis (n=58)	AS, women only (n=20)	AS, B27 positive only (n=205)	AS, B27 negative only (n=28)	Healthy controls (n=228)
Gm phenotype								
Gm(1;21)	2.5	3.6	0	5.2	5.0	2.4	0	3.5
Gm(1,2;21)	8.8	14.5†	31.3‡	8.6	15.0	9.8	3.6	3.5
Gm(1,2;5,21)	0.8	1.8	0	1.7	0	1.0	0	0
Gm(1,2,3;5,21)	12.9	7.3	0	17.2	10.0	9.3	29.3	18.9
Gm(1,3;5,21)	26.7	18.2	25.0	24.1	20.0	26.3	28.6	25.4
Gm(3;5)	48.3	54.5	43.8	43.1	50.0	51.2	28.6	48.7
Gm haplotype								
Gm ^{1,21}	38.8	38.2	56.3	37.9	40.0	39.5	32.1	32.5
Gm ^{1,2;21}	22.5	23.6	31.3	27.6	25.0	20.0	42.9	22.4
Gm ^{3,5}	87.9	80.0	68.8§	84.5	80.0	86.8	96.4	93.0
Gm homozygous	50.8	58.2	43.8	11.1	55.0	53.7	28.6	52.2
Gm heterozygous	49.2	41.8	56.3	48.9	45.0	46.3	71.4	47.8

*Only wrist, metacarpophalangeal, and interphalangeal joints, ankle, or forefoot affected.

†Odds ratio when compared with healthy controls 4.7; corrected p (p_c)<0.05.

‡Odds ratio when compared with healthy controls 12.5; p_c<0.0005.

§Odds ratio when compared with healthy controls 0.17; p_c<0.04.

||Odds ratio when compared with B27-negative group 0.16; p_c<0.0005.

patients with peripheral arthritis, especially of the distal type. In the previous reports such a relation was not observed,^{18,19} probably owing to the lower number of cases studied.

It could be argued that, compared with previous reports,^{18,19} our patients with AS may have more signs of other rheumatic diseases, e.g., psoriatic arthritis or rheumatoid arthritis, thus giving rise to the Gm allele frequency deviations not detected by others. The exclusion of patients with psoriasis and inflammatory bowel diseases as well as the small number of patients with family histories of psoriasis or with rheumatoid factor (see 'Patients and controls') make this kind of selection bias less likely, however. Moreover, if the patients with rheumatoid factor or a family history of psoriasis were excluded the Gm(1,2;21) frequency in our patient group would rise as none of these 10 patients had the Gm(1,2;21) phenotype.

In the patient subgroup with anterior uveitis we did not observe any increased frequency of Gm phenotypes, in contrast with a previous report.²³

The difference in Gm(1,2,3;5,21) frequency between B27 positive and negative patients with AS further accentuates the genetic heterogeneity of AS. In HLA-B27 negative patients with AS other genetic factors may play a part, e.g., other HLA antigens, as described in some previous reports²⁴⁻²⁷ but not in others,²⁸ or Gm(1,2,3;5,21), as found in this study.

The Gm(1,2;21) phenotype shown here as a marker for peripheral arthritis in AS is also associated with HLA-DR4 positive rheumatoid arthritis (RA), as published previously.¹⁵ In this context the report of Miehle *et al.*²⁹ though not confirmed by others,³⁰⁻³² has to be mentioned. These authors described an association of distal peripheral arthritis in AS with HLA-DR4, which is also known to be linked with RA. Despite these genetic similarities between RA and distal peripheral arthritis in AS, the distal peripheral arthritis in our 16 patients was clinically different from the well known articular manifestations in patients with RA (see Table 1). Oligoarthritis and asymmetrical joint involvement were frequent, and only one of these 16 patients fulfilled the classification criteria for definite RA.³³ Thus the main conclusion is that an immunoglobulin G (Gm) allotype is associated in AS with peripheral arthritis, particularly distal arthritis. It has not been established whether this subgroup of AS is genetically and clinically related to RA.

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