

## HLA-A, B antigens and $\alpha_1$ -antitrypsin phenotypes in nodal generalised osteoarthritis and erosive osteoarthritis

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**SUMMARY** HLA-A, B and  $\alpha_1$ -antitrypsin phenotypes were studied in 90 unrelated patients with established nodal generalised osteoarthritis (OA). Compared with standard reference populations, independently increased frequency of the HLA-A1B8 and MZ  $\alpha_1$ -antitrypsin phenotypes were observed (27% v 11.5%, relative risk 2.79, and 12% v 3.6%, relative risk 3.73 respectively). These associations related to development of nodal generalised OA rather than to severity as judged by the summated radiographic scores for hand OA. Ten patients had marked subchondral radiographic erosions and were further classified as erosive OA; these patients had an increased frequency of the MS  $\alpha_1$ -antitrypsin phenotype (30% v 9%) and higher radiographic OA scores corrected for presence of erosions. This first report of two independent genetic markers in nodal generalised OA is of interest in relation to the increasingly recognised inflammatory component of the osteoarthritis process.

Symptomatic osteoarthritis (OA) is a common but ill understood condition with a spectrum of clinical presentation and outcome.<sup>1,2</sup> Multiple factors (genetic, constitutional, environmental) may be involved in its development.<sup>3-5</sup> To understand better its pathogenesis OA has been divided into subsets on the basis of distribution, radiographic features, associated crystal deposition, and recognised aetiological factors.<sup>2</sup> Nodal generalised OA is a subset characterised by polyarticular interphalangeal and thumb base OA, female preponderance, early inflammatory component, and Heberden node formation<sup>6</sup>; of all OA subsets, familial tendency is particularly recognised.<sup>4</sup> Erosive OA is an uncommon form of generalised OA sharing many features of nodal generalised OA but differing by having marked subchondral erosive change and a florid inflammatory component.<sup>7,8</sup>

Genetic factors have been extensively studied in rheumatic diseases<sup>4</sup> and may be associated with either development or severity.<sup>9-12</sup> Despite marked familial predisposition few studies have investigated

genetic markers in nodal generalised OA.<sup>4</sup> Only four report the frequencies of HLA antigens, with conflicting results<sup>13-16</sup>; one reporting increased frequency of HLA-A1B8,<sup>13</sup> one an increased frequency of HLA-B8,<sup>14</sup> and two finding no associations.<sup>15,16</sup> To our knowledge  $\alpha_1$ -antitrypsin phenotypes, well studied in other rheumatic diseases,<sup>17-21</sup> have not been examined in OA.

We therefore investigated the prevalence of HLA-A, B antigens and  $\alpha_1$ -antitrypsin phenotypes in patients with well characterised nodal generalised OA to define genetic markers predisposing to either OA development or severity of radiographic change.

### Patients and methods

Ninety unrelated, English born, white patients (79 women, 11 men; mean age 67, range 42-90 years) presenting to the Nottingham unit with nodal generalised OA were studied. Each had symptomatic polyarticular interphalangeal OA affecting more than three rays of each hand with Heberden node formation unrelated to obvious trauma. Each underwent full clinical and radiographic assessment. All had radiographic and in some cases additional clinical evidence of OA at other sites, but no

attempt was made to subclassify further in terms of patterns of joint involvement. Twenty three patients had chondrocalcinosis (14 with synovial fluid confirmation of calcium pyrophosphate dihydrate crystals); six others had synovial fluid calcium pyrophosphate dihydrate crystals but no chondrocalcinosis. Apart from OA there was no evidence of additional rheumatic disease in any patient.

Plain anteroposterior hand radiographs were examined blind by two observers. Individual osteoarthritic features (osteophyte, joint space loss, sclerosis, cysts) were scored 0-3 for each joint examined; subchondral erosion, bone attrition, or remodelling were scored 1 if present. Each proximal and distal interphalangeal, metacarpophalangeal, carpometacarpal, scaphotrapezial, and radiocarpal joint in each hand was scored using this system (modified from Thomas *et al*<sup>22</sup>). Scores of both hands were summated for each patient. Those with marked subchondral erosions in three or more rays of each hand were classified as erosive OA: less widespread or equivocal subchondral erosive change did not qualify.

Eleven HLA-A and 15 HLA-B antigens were determined by standard lymphocytotoxic techniques<sup>23</sup> using well characterised antisera (National Blood Transfusion Centre, Sheffield).  $\alpha_1$ -Antitrypsin

phenotypes were determined by isoelectric focusing in polyacrylamide gel<sup>24</sup>: this allows identification of M (1 and 2), S, Z, and P phenotypes. Serum  $\alpha_1$ -antitrypsin concentrations were determined by radial immunodiffusion.<sup>25</sup> Two standard reference populations were used for comparison: the HLA reference population comprised 2041 kidney donors<sup>26</sup> representing the indigenous United Kingdom population (in Hardy-Weinberg equilibrium); the  $\alpha_1$ -antitrypsin controls were 2000 blood donors from the same (Midlands) region of England.<sup>27</sup>

#### STATISTICS

Comparison of frequencies was by  $\chi^2$  test using Yates's continuity correction. A corrected significance level ( $p_c$ ) was obtained for HLA and  $\alpha_1$ -antitrypsin frequencies by multiplying the p value by the number of variables examined.<sup>28</sup> Differences in graded data were compared by Wilcoxon rank sum test. Association between variables was by correlation coefficient.

#### Results

In the 90 patients the mean duration of hand symptoms was 11 (range 1-38) years. Ten patients (nine female, one male; mean age 70, range 53-90

Table 1 Prevalence of individual HLA antigens in the study and in the reference population

HLA antigens	Patients with NGOA* (n=90) No (%)	Reference population (n=2041) (%)	$\chi^2$	p Value	$p_c$
A1	35 (39)	33	0.44	NS	
A2	47 (52)	50	0.03	NS	
A3	14 (16)	28	0.19	NS	
A9	16 (18)	18	0.05	NS	
A10	7 (8)	8	0.11	NS	
A11	13 (14)	12	0.08	NS	
A28	3 (3)	7	2.11	NS	
A29	6 (7)	9	0.74	NS	
A30/31	5 (6)	10	1.97	NS	
A32	2 (2)	8	4.44	<0.05	NS
B5	4 (4)	8	1.70	NS	
B7	24 (27)	29	0.05	NS	
B8	28 (31)	26	0.38	NS	
B12	24 (27)	32	0.93	NS	
B13	1 (1)	5	3.79	NS	
B14	1 (1)	8	6.63	<0.01	NS
B15	8 (9)	13	1.29	NS	
B17	5 (1)	8	0.91	NS	
B18	4 (4)	7	1.13	NS	
B21	2 (2)	5	1.96	NS	
Bw22	4 (4)	5	0.27	NS	
B27	4 (4)	8	1.70	NS	
B35	6 (7)	12	0.14	NS	
B37	1 (1)	3	1.99	NS	
B40	10 (12)	14	0.67	NS	

\*NGOA=nodal generalised osteoarthritis.

years) had erosive OA (five with chondrocalcinosis and synovial fluid calcium pyrophosphate dihydrate crystals).

#### HLA ANTIGENS

Table 1 shows the prevalence of individual HLA antigens in the study and in the reference population. There was no excess of any individual HLA antigen in the group with nodal generalised OA: although HLA-A32 and B14 appeared less common in these patients, the corrected *p* value showed no difference between study and reference populations.

The phenotype A1B8, however, occurred in 24 patients with nodal generalised OA (27%) compared with 11.5% of controls ( $\chi^2=9.42$ , *df*=1, *p*=0.002, *p<sub>c</sub>*=0.004), giving a relative risk of 2.79. Comparison of patients with or without A1B8 showed no difference in age, sex, symptom duration, or summated radiographic score (Table 2). Distribution of A1B8 was the same for those with or without chondrocalcinosis/calcium pyrophosphate dihydrate deposition ( $\chi^2=0.85$ , *df*=1, *p*=0.36).

#### $\alpha_1$ -ANTITRYPSIN PHENOTYPES

Eleven (12%) patients with nodal generalised OA had MZ phenotype compared with 3.6% of controls ( $\chi^2=12.9$ , *df*=1, *p*=0.0004, *p<sub>c</sub>*=0.0012), giving a relative risk of 3.73. Comparison of patients with nodal generalised OA with or without this phenotype showed no difference in age, sex, symptom duration, or radiographic score (Table 2): serum  $\alpha_1$ -antitrypsin concentrations were not significantly lower in those with MZ. No other differences in  $\alpha_1$ -antitrypsin phenotypes were found (Table 3). Distribution of MZ was the same for those with or without identified crystal deposition ( $\chi^2=0.03$ , *df*=1, *p*=0.18).

MZ and A1B8 phenotypes were independent associations within patients with nodal generalised OA, two only showing concurrence ( $\chi^2=1.09$ , *df*=1, *p*=0.29).

#### FINDINGS IN EROSIIVE OA

The 10 patients with erosive OA had higher radiographic OA scores, even after correction for

Table 2 *Characteristics of patients with nodal generalised osteoarthritis, with separate analysis for those with or without the A1B8 haplotype and  $\alpha_1$ -antitrypsin phenotype*

	All patients	A1B8 Haplotype		MZ Phenotype	
		Present	Absent	Present	Absent
No (%)	90 (100)	24 (27)	66 (73)	11 (12)	79 (88)
Age (years)					
mean	67	65	70	71	67
(range)	(42-90)	(42-88)	(47-88)	(60-88)	(42-90)
M:F	1:7.2	1:5.0	1:8.4	1:4.5	1:7.8
Duration of symptoms (years)					
mean	11	10	11	11	11
(range)	(1-38)	(1-38)	(1-30)	(1-20)	(1-38)
Summated radiographic score					
mean	94	94	95	109	92
(range)	(19-227)	(19-227)	(22-176)	(39-227)	(19-198)
Concentration of $\alpha_1$ -anti-trypsin (g/l)					
mean	1.7	1.6	1.7	1.4	1.7
(range)	(0.9-4.3)	(1.0-2.6)	(0.9-4.3)	(1.0-2.0)	(0.9-4.3)

Table 3  *$\alpha_1$ -Antitrypsin phenotypes in patients with nodal generalised osteoarthritis and in the reference population*

Phenotype	Patients with NGOA*	Reference population (%)	$\chi^2$	<i>p</i> Value	<i>p<sub>c</sub></i>
	No (%)				
M	68 (76)	84.2	2.67	NS	
S	10 (11)	9.8	0.05	NS	
Z	11 (12)	3.6	12.9	0.0004	0.0012
V	1 (1)	1			

\*NGOA=nodal generalised osteoarthritis.

Table 4 Characteristics of patients with erosive and non-erosive nodal generalised osteoarthritis

	Erosive	Non-erosive	p Value	$p_c$
No (%)	10 (11)	80 (89)		
Age (years)				
mean	70	70	NS	
(range)	(53-90)	(42-88)		
M:F	1:9	1:7	NS	
Duration of symptoms (years)				
mean	18	10	<0.05	
(range)	(3-38)	(1-30)		
Summated radiographic score				
mean	148	90	<0.001	
(range)	(101-227)	(19-167)		
Corrected radiographic score				
mean	141	90	<0.001	
(range)	(95-220)	(19-167)		
Concentration of $\alpha_1$ -antitrypsin (g/l)				
mean	1.9	1.6	NS	
(range)	(0.9-4.3)	(0.9-3.2)		
A1B8 haplotype (No (%))	3 (30)	21 (26)	NS	
$\alpha_1$ -Antitrypsin phenotype (No (%))				
M only	6 (60)	62 (78)	NS	
Z	1 (10)	10 (13)	NS	
S	3 (30)	7 (9)	<0.001	<0.001

presence of erosions (Table 4,  $p < 0.001$ ). Patients with erosive or non-erosive OA showed no difference in age, sex, frequencies of HLA antigens, A1B8 phenotype, or serum  $\alpha_1$ -antitrypsin concentrations but MS  $\alpha_1$ -antitrypsin phenotype was more common in those with erosive OA ( $p_c < 0.001$ ). Although patients with erosive OA had longer duration of symptoms ( $p < 0.05$ ), this did not correlate with the radiographic score ( $r = 0.16$ ,  $t = 0.46$ ,  $df = 8$ ,  $p > 0.50$ ).

## Discussion

Although the pathogenesis of OA is poorly understood, multiple factors, including genetic predisposition, are likely to be involved.<sup>29</sup> Nodal generalised OA is a subset with obvious familial tendency and was therefore chosen for the present study. Definition and characterisation of OA, however, are problematic,<sup>30, 31</sup> and diagnostic criteria for individual subsets have not been agreed. We included only patients with symptomatic polyarticular interphalangeal OA and Heberden's nodes (nodal generalised OA): such hand involvement is generally accepted as the marker for predisposition to generalised OA. Some, in addition, had florid subchondral erosive change and were further classified as erosive OA.<sup>7, 8</sup> Selection of appropriate controls in such a study is problematic but of obvious paramount importance. In the United Kingdom clustering of HLA and  $\alpha_1$ -antitrypsin

phenotypes occurs in certain, defined, geographically isolated, or ethnically separated groups.<sup>26, 32</sup> No patient or control fell within such groups, however: controls for  $\alpha_1$ -antitrypsin were from the same Midlands region<sup>27</sup>; HLA control data were derived from a large collaborative study representative of United Kingdom subjects.<sup>26</sup> To reduce further the chance of spurious associations resulting from examination of a large number of variables a corrected significance value was used.<sup>28</sup>

Although no individual HLA-A or B antigen was present in excess, patients with nodal generalised OA had an increased frequency of HLA-A1B8 phenotype. This concurs with Lawrence *et al*, who examined 32 male probands and 91 relatives, reporting an increased frequency of A1B8 but no association with ABO or rhesus blood group antigens.<sup>13</sup> The increased frequency of HLA-B8 reported by Brodsky *et al*<sup>14</sup> relates to 40 Belgian patients selected for Heberden's nodes alone. Isolated Heberden's nodes show genetic predisposition separate from nodal generalised OA,<sup>33</sup> however, and differences between our study and that of Brodsky *et al* (and of two reporting no HLA association<sup>15, 16</sup>) may result from variability in patient characterisation rather than from true genetic differences. We also demonstrated an increased frequency of MZ  $\alpha_1$ -antitrypsin phenotype. Increased frequency of MZ has been associated with rheumatoid arthritis,<sup>18</sup> ankylosing spondylitis,<sup>19</sup> and juvenile chronic polyarthritis,<sup>34</sup> but this is the

first report of an increased frequency of  $\alpha_1$ -antitrypsin phenotype in OA. Identification of two such independent associations supports the clinically derived suggestion of polygenic inheritance.<sup>4</sup> Lack of association between A1B8 and MZ is not unexpected; genes for these products are widely separated, HLA antigens being encoded on chromosome 6 and  $\alpha_1$ -antitrypsin on chromosome 14 near the Gm locus for IgG.<sup>35</sup>

HLA-A1B8 phenotype is in linkage disequilibrium with DR3,<sup>36</sup> and commonly associates with conditions in which an autoimmune component is recognised—for example, systemic lupus erythematosus,<sup>37</sup> autoimmune thyroid disease,<sup>38</sup> and Sjögren's syndrome.<sup>37</sup> Female preponderance and influence of hormonal factors on disease expression are common to several such conditions. Symptomatic nodal generalised OA predominantly affects women, with frequent onset around the menopause ('menopausal arthritis'<sup>39</sup>) and it is tempting to speculate that autoimmune mechanisms may be incriminated. Support comes from reported associations between erosive OA and Sjögren's syndrome,<sup>40</sup> immunohistological examination of osteoarthritic synovium and cartilage,<sup>41 42</sup> the prevalence of rheumatoid factor in nodal generalised OA,<sup>43</sup> and the increasingly recognised clinical inflammatory component.<sup>44</sup> Association with MZ phenotype is also of interest in relation to possible pathogenesis. Relative deficiency of  $\alpha_1$ -antitrypsin could enhance enzyme related connective tissue damage. Although individuals with MS and MZ variants have lower serum concentrations of protease inhibitor (80% and 60% respectively) than the normal MM phenotype,<sup>45</sup> occurrence of normal  $\alpha_1$ -antitrypsin concentrations and similar radiographic scores in the present series suggests that this association reflects genetic linkage rather than involvement of protease inhibitor deficiency.

The HLA-A1B8 and MZ  $\alpha_1$ -antitrypsin associations appear to relate to nodal generalised OA development rather than severity, as judged by radiographic assessment. In the small group of patients with erosive OA, in whom MS phenotype may be more frequent, radiographic scores were greater, and the possibility that MS relates to more severe damage warrants further study. Although erosive OA is a recognised subset,<sup>7 8</sup> lesser degrees of erosive change are not uncommon and may be difficult to identify in remodelled joints. Erosive OA may thus represent one end of a spectrum rather than a discrete category.

Although this study was confined to patients with nodal generalised OA and erosive OA, clear separation between subsets or 'primary' and 'secondary' forms is not distinct.<sup>29</sup> Furthermore, asymptomatic

OA is common, showing increasing prevalence with age.<sup>46</sup> It is possible that similar genetic factors may associate with other forms of symptomatic OA, but unlikely that they relate to development of the osteoarthritic process itself. Studies of patients with non-nodal generalised OA are required to determine whether such factors associate primarily with hand involvement, with multifocal or polyarticular distribution, or with a tendency for the usual asymptomatic process to 'decompensate' and manifest as symptomatic arthritis.

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