Inflammatory Eye, Skin, and Bowel Disease in Spondyloarthritis: Genetic, Phenotypic, and Environmental Factors

SINEAD BROPHY, STEPHAN PAVY, PETER LEWIS, GORDON TAYLOR, LINDA BRADBURY, DUNCAN ROBERTSON, CHRIS LOVELL, and ANDREI CALIN

ABSTRACT. ***Objective.*** To explore the nature of the interrelationship between inflammatory disease of the spine/joints, skin, eye, and bowel [i.e., ankylosing spondylitis (AS), psoriasis, iritis, inflammatory bowel disease (IBD)].

Methods. The study used 4 approaches: (1) analysis of the prevalence of secondary disorders within the AS individual (chi-square and matched pair analysis); (2) study of the temporal relationship between the onset of the different conditions; (3) evaluation of the prevalence of disease among first degree relatives; and (4) influence of secondary disorders on outcome of AS.

Results. 1. Among 3287 patients with AS, more than expected had either spondylitis associated with multiple co-disorders or pure AS (with no co-diseases); fewer than expected had AS plus a single co-disease (chi-square = 32.2, $p < 0.001$). In a matched pair analysis, patients with AS and a secondary disorder were more likely to have an additional concomitant disease, e.g., IBD-AS (n = 335) patients had a higher prevalence of iritis [45.4% vs 36.7%; OR 1.4 (1.1-2.0)] or psoriasis [23.9% vs 14.3%; OR 1.9 (1.3-2.8)] than controls. 2. Among our database subjects, the symptomatic onset of the spinal disease precedes or is contemporaneous with gut, skin, and eye involvement (matched pair t test, $p < 0.001$). 3. Patients with multiple disorders predict the highest prevalence of co-diseases (i.e., psoriasis, IBD, iritis, or AS) within family members, followed by those AS patients with only IBD, psoriasis, or iritis in descending order. 4. Both psoriasis and IBD increase severity in terms of function and disease activity of AS in the patient. Radiological change is greatest for those AS subjects with iritis.

Conclusion. There is a striking overlap within patients and family members of rheumatological, dermatological, and gastroenterological diseases. The susceptibility genes of these co-disorders appear to overlap with each other and with AS: 1. A patient with 2 inflammatory conditions is at an increased risk of developing an additional related inflammatory disorder. 2. Those with enteropathic spondylarthritis would appear to carry the greatest genetic load in terms of first degree relatives developing inflammatory conditions (including psoriasis and iritis that are not seen in the index IBD-AS patient). 3. The secondary disorders do not precede AS (arguing against psoriasis and IBD allowing for an environmental conduit to pathogenic triggers in AS). The susceptibility factors for these inflammatory conditions may be additive or have a synergistic effect on each other. There is evidence for a shared gene hypothesis. (J Rheumatol 2001;28:2667–73)

Key Indexing Terms:
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From the Epidemiology Department, Royal National Hospital for Rheumatic Diseases, Bath, UK.

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S. Brophy, PhD, Research Assistant; S. Pavy, MD, Research Fellow, Epidemiology Department, Royal National Hospital for Rheumatic Diseases; P. Lewis, PhD, MBCS, CEng, Senior Lecturer, Biostatistics; G. Taylor, DPhil, MSc, BSc, Biostatistician, School of Postgraduate Medicine, University of Bath; L. Bradbury, RGN, Research Nurse, Wellcome Trust Centre for Human Genetics, Oxford University, Oxford; D. Robertson, MD, FRCP, Consultant Gastroenterologist, Department of Gastroenterology; C. Lovell, MD, FRCP, Consultant Dermatologist, Department of Dermatology, Royal United Hospital, Bath; A. Calin, MD, FRCP, Consultant Rheumatologist, Epidemiology Department, Royal National Hospital for Rheumatic Diseases.

Address reprint requests to Dr. A. Calin, Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath, BA1 1RL, UK. E-mail: andrei.calin@virgin.net

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The spondyloarthritides are a group of disorders characterized by involvement of the sacroiliac joints and peripheral inflammatory arthropathy together with target organs including the eye, bowel, and skin[1]. Patients with ankylosing spondylitis (AS) can develop psoriasis or inflammatory bowel disease (IBD), whereas those with psoriasis or enteropathy may develop joint involvement. The link between these diseases might be genetic, with shared susceptibility genes. This hypothesis is supported by the finding that HLA-B27 negative spondylitis patients are more likely to have secondary forms of disease linked to psoriasis or IBD[2]. Thus, in the absence of the B27 susceptibility effect, genes such as those for the other inflammatory conditions may be important in predisposing the individual to AS. Alternatively, these conditions may be linked by environmental factors, the inflamed gut and skin allowing the conduit of pathogenic triggers that induce AS. The HLA-

B27 transgenic rat develops clinical features including: inflammatory gastrointestinal disease, skin lesions, spinal lesions, and peripheral arthritis[3]. These rats generally develop bowel inflammation, which is then followed by arthritis. However, if the HLA-B27 transgenic rat is maintained in a sterile environment neither the inflammatory gastrointestinal disease nor the arthritis develops[4].

Thus there is evidence that the link between these inflammatory conditions could be genetic or environmental. How these diseases are linked will have an important influence on our understanding and treatment of AS and the associated risks to relatives of affected individuals[5]. This study explores the nature of the interrelationship between inflammatory disease of the spine/joints, skin, eye, and bowel (i.e., AS, psoriasis, iritis, IBD).

MATERIALS AND METHODS

The database. The Bath Royal National Hospital Rheumatic Disease (RNHRD) Ankylosing Spondylitis Database consists of 4953 patients. These subjects are defined as those with symptomatic disease and sacroiliitis diagnosed by radiography, fulfilling the New York criteria for AS (i.e., all patients had at least sacroiliitis stage II bilateral or stage III unilateral disease) and meeting the Amor (1991) and the European Spondylarthropathy Study Group diagnostic criteria for the spondyloarthropathies. These patients represent a subgroup of spondyloarthritis, as they only include patients diagnosed with AS. Subjects are either those referred to the RNHRD or are members of the National Ankylosing Spondylitis Society (NASS). Among the patients, 1915 (39%) have iritis, 811 (16%) psoriasis, and 404 (8%) IBD (158 Crohn's disease and 246 ulcerative colitis). The diagnoses for iritis and psoriasis were ascertained by the general practitioner, rheumatologist, ophthalmologist, or dermatologist. A gastroenterologist was required for the diagnosis of IBD. In each case the diagnosis was recorded as representing one point in time. Two studies have been performed to validate the diagnosis of AS in those patients recruited through NASS. One hundred forty-six subjects were assessed by a rheumatologist and 100% were confirmed as having AS according to the New York Criteria (personal communication, M. Brown, Oxford). The general practitioners (GP) of a further 240 NASS members were contacted to determine whether their patients' AS had been confirmed radiologically. In 229 (95.4%) cases, AS with radiological evidence of sacroiliitis was confirmed. We contacted the GP of 120 psoriasis-AS patients and 139 IBD-AS patients. Of these, 77 (64%) and 112 (81%) replied confirming psoriasis in 65 (84%) of cases and IBD in 108 (96%) of cases. Iritis was diagnosed by an eye specialist in 1551 (81%) cases of 1915 reported with iritis (GP or rheumatologist diagnosed 19%).

Data processing and statistical methods. Of the 4953 subjects on the database, 3287 had a complete data set with full family and personal data (the disease duration and sex ratio of those analyzed compared to those without complete records was comparable: 21.3 yrs, 2.3:1 M:F and 20.0 yrs, 2.1:1 M:F, respectively). The prevalence of the 3 individual secondary disorders (psoriasis, IBD, iritis) was determined. From these data the expected numbers of patients with none, one, 2, or 3 of these conditions was established assuming independence between the diseases. The expected number was compared with the observed number using the chi-square test. Patients with a secondary disorder were matched with an available and appropriate control (without the specific condition) for disease duration, age, and sex [i.e., psoriasis patients were matched with those without psoriasis (600 pairs of 811 psoriasis patients), IBD patients with those without IBD (335 pairs of 404 IBD patients), and iritis patients with those without iritis (735 pairs)]. All pairs were matched for exactly the same number of years of disease duration and age. These pairs were compared using McNemar's chi-square for prevalence of secondary disorders as outlined above.

Patients with a confirmed diagnosis for all reported secondary conditions and arthritis were asked to report when symptoms of each condition first began. Patient recollection was verified by GP reports. Patients with a confirmed diagnosis of disease were asked, "to your knowledge do any members of your family have a diagnosis of psoriasis, inflammatory bowel disease, iritis or ankylosing spondylitis." Patients with multiple disease completed disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[6]] and function [Bath Ankylosing Spondylitis Functional Index (BASFI)[7]] assessments. (Three assessments were made on each patient. The results of the last assessment were used as these were completed in the same month by all subjects.) The radiographs of RNHRD patients (n = 660) were blindly scored by 2 independent observers using the Bath Ankylosing Spondylitis Radiology Index (BASRI[8]) and then subgrouped according to presence of secondary disorders. Matched pair t tests were used to compare groups.

RESULTS

Prevalence of secondary disorders within the individual. There were more people with spondylitis and multiple co-diseases (i.e., more than one secondary disorder) than expected and more with pure AS (i.e., no secondary diseases), but there were fewer with spondylitis and only one single co-disease than expected. The observed/expected numbers for patients with no co-diseases were 2069/1973, with one co-disease 1722/1872, with 2 co-diseases 454/417, and with 3 co-diseases 42/25 (chi-square = 32.2, $p < 0.001$).

Psoriatic patients had a higher prevalence of iritis, 48% versus 40% [odds ratio (OR) 1.4, 95% confidence interval (95% CI 1.1-1.7)] and more IBD than controls (OR 1.3, 95% CI 1.1-2.0), 12.5% vs 9.4%. Demographic data were as follows: psoriasis and controls [number, sex ratio, disease duration (SD), age (SD)] n = 600, M:F 3.2:1, disease duration = 22 (10) years, age = 47 years (11).

Iritis patients had a higher prevalence of psoriasis [OR 1.4 (1.1-1.8)] 18.2% vs 14% and IBD [OR 1.5 (1.1-2.2)] 10.6% vs 7.3% than controls. Demographic data: Iritis and controls [number, sex ratio, disease duration (SD), age (SD)] n = 735, M:F = 2.3:1, disease duration = 21 (10) years, age = 45 (11) years.

IBD patients had a higher prevalence of iritis [OR 1.4 (1.1-2.0)] 45.4% vs 36.7% and psoriasis [OR 1.9 (1.3-2.8)] 23.9% vs 14.3% than controls. Demographic data: IBD and controls [number, sex ratio, disease duration (SD), age (SD)] n = 335, M:F = 2.3:1, disease duration = 22 (10) yrs, age = 47 (11) yrs.

Temporal relationship between onset of the different conditions. Patient recollection of age of onset of symptoms and diagnosis was confirmed using GP reports. The GP and patient recollection was comparable for age/year in 95% of cases of AS, IBD, and psoriasis and 100% of those with iritis. [There were 47 patients with psoriasis for whom the GP had records of when first symptoms presented. Of these 45 (i.e., 95%) reported the same year of presentation as the patient recalled. There were 110 patients with IBD where the GP had records and verified the patient recollection as

correct in 105 (95%) of these cases. In the sample with iritis only, 58 GP had records (as patients may generally present directly to emergency or the eye department and not to the GP), of these all 58 were in the same year as given by the patient. However, many of the GP for the non-included samples reported that results had been computerized and the data were not available or the patient was new and there were no backdated records.] Onset of AS symptoms occurs significantly before advent of iritis ($p < 0.001$) and IBD ($p < 0.001$) symptoms. Onset of psoriasis and AS symptoms occurs at comparable ages. Gut, skin, and eye symptoms do not precede those of AS (Table 1).

Prevalence of disease among first degree relatives. Relatives of patients with IBD-AS are at an increased risk of developing psoriasis and iritis (Table 2 and Figure 1). Those with multiple disease predict the highest prevalence of co-diseases (i.e., psoriasis, IBD, iritis, or AS) within family members, followed by those with IBD, psoriasis, and lastly iritis.

Influence of secondary disorders on outcome of AS. Disease activity and function are worse for patients with psoriasis and/or IBD. However, those with iritis are comparable to those with primary disease (Table 3). Radiological change was worse for those with iritis than for patients with pure AS (Table 4).

DISCUSSION

Our data explore the nature of the interrelationship between the spinal disease AS and the extraspinal co-disorders. We are particularly intrigued by the relative role of environment and genetics in the interrelationship of these inflammatory disorders. We have shown that: (1) in an individual with AS, the presence of one concomitant disorder enhances the probability of there being a second or third co-disease; (2) the symptoms of AS precede or are contemporaneous with the concomitant disorders; (3) family members are at increased risk of secondary disorders even in the absence of their expression in the index case; and finally (4) the expression of severity (i.e., BASRI, BASDAI, BASFI) in AS is influenced by the presence of the secondary conditions. Thus, it can be concluded that the susceptibility genes of these co-disorders overlap with each other and with AS and affect disease severity.

Table 1. Mean age of onset of the inflammatory disorders [iritis (I), psoriasis (Ps), inflammatory bowel (IBD)] compared to onset of ankylosing spondylitis (AS) (all cohorts are independent and do not include subsets of the same individuals).

	AS (yrs)	Iritis (yrs)	Psoriasis (yrs)	IBD (yrs)	Mean difference (CI)
Pure AS, n = 2221*	25				
AS + I, n = 151	23	33			AS vs I: 10 (7.4–10.8)
AS + Ps, n = 40	27		26		AS vs Ps: none
AS + IBD, n = 74	24			30	AS vs IBD : 6 (3.4 –9.7)
AS + I + Ps, n = 30	28	39	32		AS vs I: 11 (6.6–15.2), AS vs Ps: 4 (0.5–8.8)
AS + I + IBD, n = 66	22	34		31	AS vs I: 12 (9.6–15.8), AS vs IBD: 9 (5.1– 12.2)
AS + Ps + IBD, n = 18	23		26	31	As vs Ps: none, AS vs IBD: 6.6 (1.7– 11.6)
As + I + Ps + IBD, n = 26	23	32	33	33	As vs I: 9 (4.5–14.8), AS vs Ps: 10 (2.5– 16.9), AS vs IBD: 10 (3.6–16.1)

* Includes original 2069 and additional recruited subjects.

Table 2 . First degree relatives†.

	Ps, %	IBD, %	Iritis, %	AS, %	Order
1. Pure AS , n = 138	10	7	6	25	1
2. AS + iritis, n = 142	5	3	13	29	2
3. AS + Ps, n = 42	33	12	0	14	3
4. AS + iritis + Ps, n = 26	19	8	15	19	4
5. AS + IBD + Ps, n = 17	12	24	6	24	5
6. AS + iritis + IBD, n = 63	14	14	16	29	6
7. AS + IBD, n = 76	17	24	8	24	6
8. AS + IBD + Ps = Iritis, n = 23	17	17	26	30	8
Population rate*	1–2	0.07–0.1	0.2**	0.25	

*From Calin A, Taurog J. The spondylarthritides. Oxford University Press;1998, and Linssen A, Rothova A, Valkenburg H, et al, editors. **The lifetime cumulative incidence of acute anterior uveitis in a normal population and its relation to ankylosing spondylitis and histocompatibility antigen HLA-B27. Invest Ophthalmol Vis Sci 1991;32:2568-78.

† Based on patient recollection only.

AS: ankylosing spondylitis; Ps: psoriasis; IBD: inflammatory bowel disease.

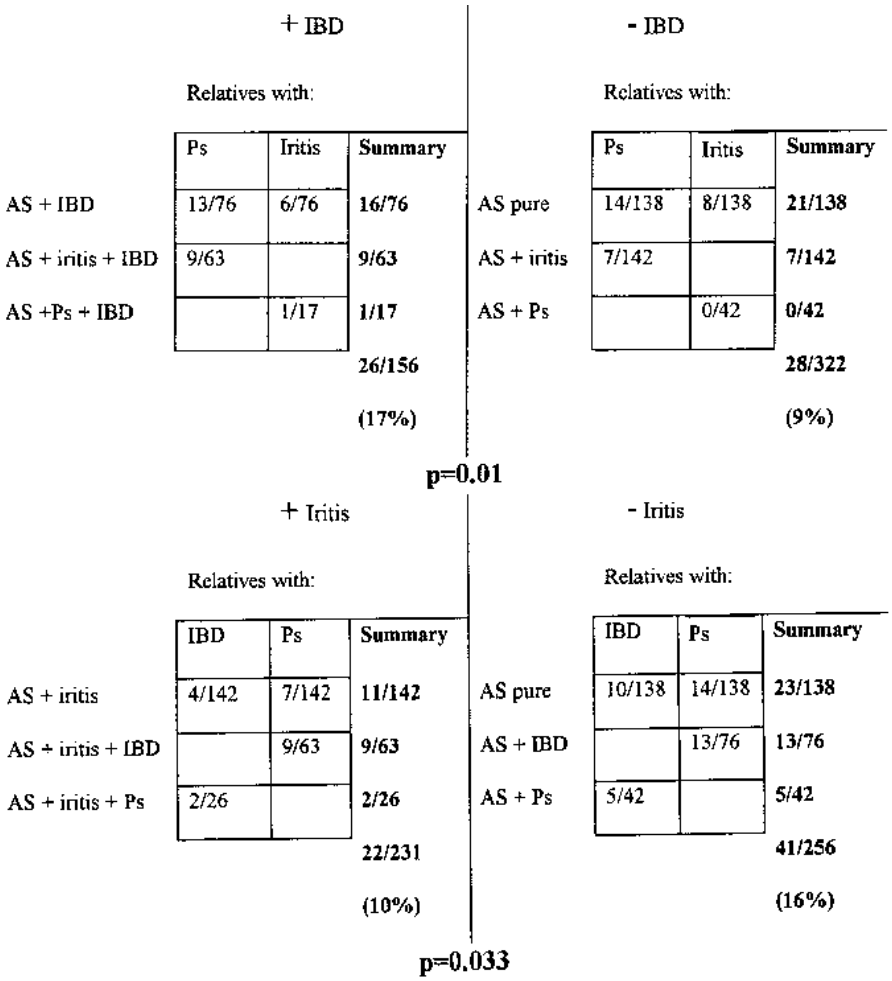

Figure 1. Relatives of ankylosing spondylitis (AS) patients with inflammatory diseases not identified in the index case.

This study is exploratory and there is no guarantee that clinical subsets will necessarily simplify the disease from a genetic perspective. In addition, in terms of the increased prevalence of secondary disorders within the individual, it is recognized that patients seen at a tertiary referral clinic may have more co-diseases than those seen in the general population. Similarly, patients who join a self-help group (NASS) may be more likely to have multiple disorders. This suggests that a bias towards multiple disease (Berkson's Bias) may be observed among the total sample. However, more patients than expected were found without a concomitant disease (pure AS) and fewer were found with AS and a single secondary disorder. This is not a finding predicted by the bias. In addition, the matched data used control and sample patients from the same population that were equally likely to have multiple disease as there were no selection differences between the subgroups (i.e., both entered the hospital/self-help group system).

A link between the secondary disorders in the absence of AS has been previously described. Psoriatic patients suffer from IBD more than controls[9], the prevalence of psoriasis is increased in Crohn's disease[10-12], and there is a higher incidence of iritis than expected among psoriasis patients[13]. Genes on chromosome 16 are associated with iritis[14], psoriasis[15], and Crohn's disease[16]. However, no gene has been identified from the region. These inflammatory disorders are linked to chromosome 6, perhaps through HLA-Cw6, in the case of psoriasis[17], B62 in IBD[18], and B27 for AS[19] and iritis[20]. Thus, there is evidence to support the finding in this study that the genetic susceptibility to inflammatory bowel, skin, eye, and joint disease overlaps and may be additive.

The suggestion that the triggering agent for AS may enter the body through the inflamed gut or skin (as proposed in the HLA transgenic rat) is not supported by our human data. There was little overt (symptomatic) inflammation due to IBD prior to the onset of symptomatic AS. However, we do appreciate that occult bowel involvement may occur early in AS[21] and that the clinical expression of psoriasis varies — very mild disease (i.e., minor scalp involvement) could be overlooked by the patient and GP. In fact, it is not known when the actual onset of disease begins in any of these conditions. It is possible that the "trigger is pulled" in the

Table 3. Phenotypic expression of secondary disease.

	AS Duration, yrs	BASDAI	BASFI	Mean Difference, 1° AS vs 2° AS [BASDAI] (CI of mean)	Mean Difference, 1° AS vs 2° AS [BASFI] (CI of mean)
Pure AS, n = 2221	19.0	4.1	3.9		
AS + I, n = 1342	23.7	3.9	4.0	NS	NS
AS + Ps, n = 389	19.3	4.7	4.6	0.5 (0.3–0.7)	0.4 (0.2–0.7)
AS + IBD, n = 341	25.7	4.5	4.8	0.4 (0.05–0.7)	0.8 (0.6–1.1)
AS + I + Ps, n = 323	25.6	4.6	4.8	0.4 (0.2–0.6)	0.8 (0.4–1.0)
AS + I + IBD, n = 150	25.3	4.3	4.6	NS	0.6 (0.2–1.1)
AS + Ps + IBD, n = 44	20.5	5.9	5.4	1.7 (1.2–2.4)	1.6 (0.9–2.4)
AS + I + Ps + IBD, n = 46	23	4.5	5.4	NS	1.5 (0.8–2.3)

CI: Confidence interval; I: iritis; Ps: psoriasis; IBD: inflammatory bowel disease.

womb and disease begins in the infant, with age of symptom onset simply a reflection of severity of disease. However, this study has not found evidence that overt and symptomatic IBD or psoriasis are involved in triggering AS (i.e., allowing the conduit of environmental pathogens to induce AS). Conceivably, the results may be different in a population chosen from a gastroenterological or dermatological clinic[22]. For example, of the 7 out of 19 patients with non-AS spondyloarthritis followed long term who went on to develop AS, all had initially presented inflammatory gut lesions. Thus, evolution of non-AS-SpA to full blown AS was associated with gut inflammation at disease onset[23]. However, the finding that onset of bowel disease and the other inflammatory conditions do not follow a temporal pattern but may occur at any time (before or after the onset of arthritis) supports the hypothesis that susceptibility genes of inflammatory skin, eye, and bowel disease may overlap with those for inflammatory joint disease.

The prevalence of disease among family members of the index case represents an estimate of the occurrence of disease within this population. The observation of familial aggregation has been previously identified[9]. Herein, we reinforce the previous observations and suggest that the strongest genetic load can be seen among the IBD-AS sufferers, with the least observed among the iritis-AS patients (Figure 1). The data from the relatives of the pure AS subjects suggest that occult genes associated with IBD and psoriasis and/or the presence of iritis genes may be required for the development of AS (Figure 2).

Patients with psoriasis and/or IBD had poorer function and greater disease activity. Psoriasis/IBD genes may have an additive effect on susceptibility to and severity of AS.

Table 4. BASRI in primary vs secondary disease.

	Matched Pairs		
	ASI [mean (SD)]	Pure AS [mean (SD)]	p
N	143	143	
M:F	3:1	3:1	
Disease duration, yrs	22 (± 9)	21 (± 10)	
Age at onset, yrs	23.7 (± 8)	25.4 (± 8)	
BASRI total	9.2 (± 3.8)	7.7 (± 3.4)	< 0.001
	AS + Ps [mean (SD)]	Pure AS [mean (SD)]	
N	91	91	
M:F	2.5:1	2.5:1	
Disease duration, yrs	21.5 (± 9.6)	21.7 (± 10.24)	
Age at onset, yrs	23.0	23.6	
BASRI total	8.7 (± 3.5)	8.8 (± 3.7)	NS
	Cohort comparison		
	AS + IBD [mean (SD)]	PureAS [mean (SD)]	
N	23	151	
Disease duration, yrs	21.3 (± 10.3)	22.3 (9.2)	
BASRI total	8.7	8.3	NS

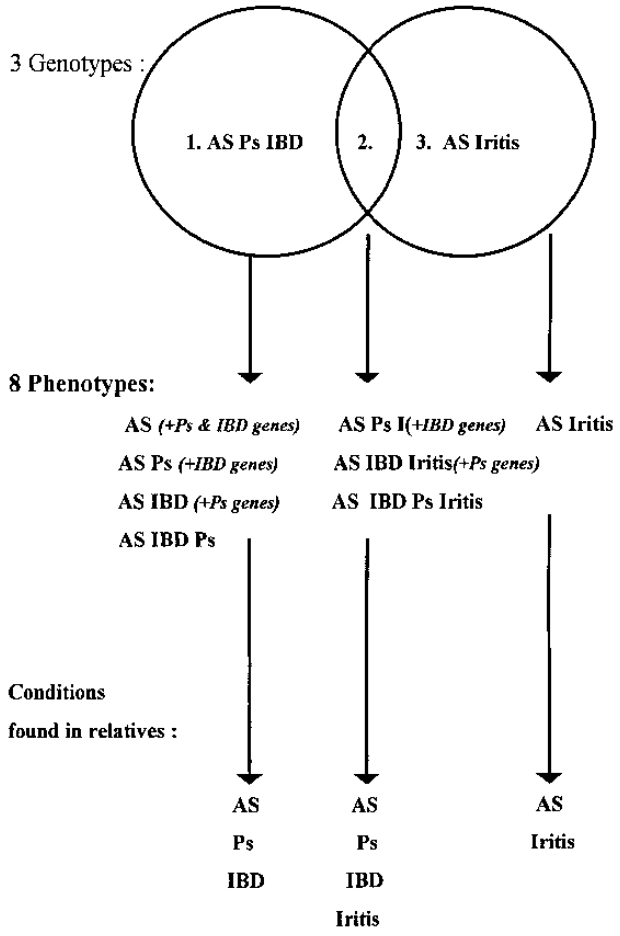

Figure 2. Relationship between AS and secondary disorders.

Alternatively, an inflammatory/immunological response to a sizeable area of body (skin surface or bowel) may have an effect of potentiating inflammation elsewhere. Indeed, it is recognized that active IBD can coincide with flares in peripheral joint disease[23]. Disease activity and function can be modified and therefore are measures of inflammation and soft tissue involvement. However, radiological assessment is measured in terms of disease-specific change and is not directly related to the level of pain/fatigue (i.e., disease activity) nor poor function (as this can be due to pain or soft tissue damage). Psoriasis/IBD does not appear to increase these disease-specific radiological changes. Conversely, iritis appears to be a strong phenotypic marker for more severe radiological disease. Moreover, peripheral arthritis in a patient with AS enhances the likelihood that iritis will develop[24].

The secondary diseases do appear to have a genetic overlap with AS in terms of susceptibility genes. The susceptibility factors for these conditions may be additive or have a synergistic effect on each other. The presence of these conditions has a pronounced effect on the phenotypic expression. The patient is more likely to have multiple disorders, develop these disorders after the onset of AS, and have a poorer outcome in terms of the spondylitis. These findings point to the striking overlap within the patient and their family of rheumatological, dermatological, and gastroenterological processes. The influence of a relevant family history is clearly revealed and the data enhance our understanding of how the shared gene hypothesis can have an effect on disease expression.

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