Genetic diagnostic profiling in axial spondyloarthritis: a real-world study

G.P. Thomas[1,2], D. Willner[1,3], P.C. Robinson[1], A. Cortes[1], R. Duan[1], M. Rudwaleit[4], N. Akkoc[5], J. Braun[6], C.T. Chou[7,8], W.P. Maksymowych[9], S. Ozgocmen[10], E. Roussou[11], J. Sieper[6,12], R. Valle-Oñate[13], D. van der Heijde[14], J. Wei[15], P. Leo[1], M.A. Brown[1,16], and the International Genetics of Ankylosing Spondylitis Consortium

[1]University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Australia; [2]Charles Sturt University, Wagga Wagga, New South Wales, Australia; [3]Australian Centre for Ecogenomics, School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane, Australia; [4]Klinikum Bielefeld and Charité University Medicine, Berlin, Germany, and Gent University, Belgium; [5]Dokuz Eylul University Hospital, Izmir, Turkey; [6]German Rheumatology Research Centre, Berlin, Germany; [7]Division of Allergy, Immunology, Rheumatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [8]School of Medicine, National Yang-Ming University, Taipei, Taiwan; [9]Department of Medicine, University of Alberta, Canada; [10]Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Erciyes University, Faculty of Medicine, Kayseri, Turkey; [11]King George Hospital, London, United Kingdom; [12]Rheumatology, Med Klinik 1, Charite, Campus Benjamin Franklin, Berlin, Germany; [13]Spondyloarthropathy Group-Division of Rheumatology, Hospital Militar Central / Universidad de La Sabana, Colombia; [14]Leiden University Medical Center, Leiden, the Netherlands; [15]Chung Shan Medical University, Taichung, Taiwan; [16]Institute of Health and Biomedical Innovation, Queensland University of Technology, Translational Research Institute, Princess Alexandra Hospital, Brisbane, Australia.

Abstract

Objective

Spondyloarthritis (SpA) is often diagnosed late in the course of the disease and improved methods for early diagnosis are required. We have tested the ability of genetic profiling to diagnose axial SpA (axSpA) as a whole group, or ankylosing spondylitis (AS) alone, in a cohort of chronic back pain patients.

Methods

282 patients were recruited from centres in the United Kingdom, Germany, Taiwan, Canada, Columbia and Turkey as part of the ASAS classification criteria for axSpA study (ASAS cohort). Subjects were classified according to the ASAS axSpA criteria, and the modified New York Criteria for AS. Patients were genotyped for ~200,000 immune-mediated disease SNPs using the Illumina Immunochip.

Results

We first established the predictive accuracy of genetic data comparing 9,638 healthy controls and 4,428 AS cases from the homogenous International Genetics of AS (IGAS) Consortium Immunochip study which showed excellent predictive power (AUC=0.91). Genetic risk scores had lower predictive power (AUC=0.83) comparing ASAS cohort axSpA cases meeting the ASAS imaging criteria with IGAS controls. Comparing genetic risk scores showed moderate discriminatory capacity between IGAS AS and ASAS imaging positive cases (AUC 0.67±0.05), indicating that significant differences in genetic makeup exist between the cohorts.

Conclusion

In a clinical setting of referred back pain patients suspected to have axial SpA we were unable to use genetic data to construct a predictive model better than that based on existing clinical data. Potential confounding factors include significant heterogeneity in the ASAS cohort, possibly reflecting the disease heterogeneity of axSpA, or differences between centres in ascertainment or classification performance.

Key words

ankylosing spondylitis, spondyloarthropathies, genetic prediction, classification criteria

Gethin P. Thomas, PhD
*Dana Willner, PhD**
*Philip C. Robinson, MBChB, PhD, FRACP**
Adrian Cortes, PhD
Ran Duan, BSc
Martin Rudwaleit, MD
Nurullah Akkoc, MD
Jurgen Braun, MD
Chung-Tei Chou, MD
Walter P. Maksymowych, FRCP(C)
Salih Ozgocmen, MD
Euthalia Roussou, MD
Joachim Sieper, MD
Rafael Valle-Oñate, MD
Désirée van der Heijde, MD, PhD
James Wei, MD
Paul Leo, PhD
Matthew A. Brown, MBBS, MD, FRACP, FAA, FAHMS

**These authors contributed equally.*

Please address correspondence to:
Prof. Matthew A. Brown,
Institute of Health and Biomedical Innovation,
Queensland University of Technology, Translational Research Institute,
37 Kent St.,
Princess Alexandra Hospital,
Woolloongabba, Qld, 4102, Australia.
E-mail: matt.brown@qut.edu.au

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Introduction

Axial spondyloarthritis (axSpA) is an inflammatory disease involving the spine, which includes both patients with radiographic sacroiliitis fulfilling the modified New York criteria of ankylosing spondylitis (AS) and patients without radiographic sacroiliitis (nr-axSpA). A key challenge is to identify those patients without radiographic sacroiliitis who will go on to develop disease. This contributes to the average delay in diagnosis of AS from onset of symptoms being 8–10 years (1, 2). The reasons for this diagnostic underperformance are manifold and include: the common nature of chronic back pain in the community, the low population prevalence of axSpA, and the long delay between onset of symptoms and changes becoming apparent on plain radiographs. Given the destructive and largely irreversible consequences of the inflammatory dysregulation in axSpA, it has long been recognised in the SpA clinical and research community that improved methods for early diagnosis are required. Patently, there is a pressing need for new approaches to diagnose disease as soon as possible after initial symptom onset and recognition.

Advances in imaging modalities, such as magnetic resonance imaging (MRI), have greatly improved the ability to identify inflammatory changes in the spine and sacroiliac joints and thus allow objective evidence of inflammation long before changes become apparent on plain radiographs (3). Even so, early diagnosis of nr-axSpA (79%/89% sensitivity/specificity) and AS with these improved methods is still imperfect and is very poor for predicting radiographic progression (100%/33% sensitivity/specificity), even when biochemical markers and co-morbidities are taken into consideration (4, 5). Clearly, there is a potential role for alternate biomarkers to assist in this process, including genetic diagnostic tests, and, potentially gene-expression profiling or proteomic-based approaches.

The Assessment of SpondyloArthritis International Society (ASAS) axSpA criteria were developed to provide classification criteria that would enable research into early diagnosis and treatment of axSpA (6, 7). This was especially aimed at facilitating studies directed towards identifying and understanding pathogenesis of early SpA and treatment strategies that might lead to disease modification.

Genetic profiling is one approach which has potential to assist in early diagnosis of axSpA; indeed *HLA-B27* typing is already included in the ASAS axSpA criteria. Since genetic profiling uses data from germline DNA sequence variation it may even be informative prior to the development of disease symptoms. The strong association of a Human Leukocyte Antigen Class I allele, *HLA-B27*, with AS has meant that its presence or absence is widely used in the diagnostic workup of axSpA. Although the association is very strong, *HLA-B27* contributes only ~20% of the heritable component of the risk of AS (8). The discovery of further multiple genetic associations is making it increasingly possible to build models that combine these markers into better performing predictive and diagnostic tests.

Most of the genetic studies to date have been performed on carefully selected homogenous cohorts. Such an approach is ideal for identifying novel genetic associations but provides little insight into the true diagnostic power of these associations. Rather these approaches need to be tested in 'real-life' clinical settings where cohorts are often heterogeneous. In this study, we tested the ability of genetic profiling to diagnose axSpA patients or a subgroup of AS patients in a cohort of chronic back pain patients classified according to the ASAS classification criteria as axSpA (including both nr-axSpA and AS) or no SpA (6, 7) based on clinical assessment, MRI scan, plain radiographs of the spine and pelvis, and tests for *HLA-B27*. Patients in this cohort were geographically diverse; collected from a number of different sites worldwide, including Britain, Canada, Germany, Colombia, Turkey and Taiwan. This very unique cohort allowed us to evaluate the utility of genetic profiling to identify axSpA and/or AS patients as well as providing an assessment of the robustness of our approach in an ethnically diverse cohort.

Table I. Summary of the features of the whole patient cohort. Percentages reflect the proportion of the cohort at that centre. '% Diagnosis axSpA' indicates the proportion meeting the ASAS axSpA criteria, and the '% AS +ve' indicates the proportion meeting the modified New York Criteria for AS.

Centre	Country	Cohort size n.	% male	Age ± SD	CRP (mg/L)	Disease Duration (yrs)	% HLA-B27+ve	% Diagnosis axSpA	% AS +ve
1	Germany	67	40	39 ± 10	5.48	8.9	66	37	22
7	Germany	20	30	41 ± 13	9.95	15.3	50	45	15
12	UK	31	29	38 ± 10	8.91	11.1	29	77	48
14	Taiwan	58	41	41 ± 11	5.06	6.0	28	60	22
17	Taiwan	19	95	27 ± 7	7.68	6.4	58	58	21
24	Canada	17	41	33 ± 8	3.41	13.7	53	47	18
31	Colombia	30	79	30 ± 8	11.21	2.0	21	59	0
34	Turkey	10	50	27 ± 6	5.72	3.5	70	40	20
35	Turkey	30	33	38 ± 9	18.62	7.0	37	90	13
All		**282**	**47**	**37 ± 11**	**8.45**	**8.21**	**43**	**57**	**20**

Materials and methods

Patient cohort

The patient cohort ('ASAS cohort') was a subset of that used in validating the ASAS axSpA classification criteria (6, 7). Briefly, for inclusion, eligible patients had to have chronic back pain (greater than 3 months duration) of unknown origin (no definite diagnosis) that began before 45 years of age, with or without peripheral symptoms, when they first presented for diagnostic work-up at the respective centre. The high frequency of *HLA-B27* (43%) (Table I) in referred patients suggests that the referring physicians suspected axSpA as the diagnosis in many subjects. To prevent selection bias, consecutive patients were recruited. Diagnostic work-up included data on gender, age, duration and age at onset of back pain, and whether it was inflammatory back pain (IBP). Response to non-steroidal anti-inflammatory drugs and the presence of extraspinal manifestations (current or in the past) was also documented. Schober's test, lateral spinal flexion and chest expansion were documented, and laboratory tests included *HLA-B27* genotyping and C-reactive protein (CRP) assays, which were carried out locally. Plain radiographs of the pelvis were taken in all patients, and sacroiliitis graded according to the modified New York criteria (mNY) by the local expert (9). At least the first 20 patients recruited at any centre received an MRI of the sacroiliac joints, and approximately 50% received an MRI of the spine.

Out of the total ASAS cohort of 694 patients, 282 patients were recruited for this genetic analysis from nine different centres in Canada, Colombia, Germany, Taiwan, Turkey, and United Kingdom. The selection of these patients was determined only by the ability to obtain blood samples for the genotyping. A summary of the features of the cohort are shown in Table I. The gender distribution, mean disease duration, proportion carriage of *HLA-B27* and mean CRP levels are similar to those of the total ASAS cohort (6, 7). We used the fulfilment of the ASAS classification criteria as gold standard for identifying axial SpA patients, not the clinical diagnosis made by the ASAS rheumatologist. This was because at different centres different criteria were used to arrive at a clinical diagnosis, as evidenced by the differing HLA-B27 prevalence between centres, and thus the findings using clinical diagnoses are subject to greater heterogeneity than using defined classification criteria. Thus, patients were classified as axial SpA or no SpA according to fulfilment of the ASAS criteria. Using the supplied clinical data, subjects were further divided into those that had AS meeting the mNY criteria.

Genetic analysis

Genotyping on the Immunochip was carried out as described previously for all samples; previous genotype data was available from the International Genetics of AS Consortium (IGAS) Immunochip project (10). Predictive model fitting was performed using the function "glm" in the R:stats package and ROC curves were generated using the R:ROCR package v. 1.0-4.

Results

Identification of significant covariates

The number of individuals of each ethnicity by centre is shown in Supplementary Table I. A significant relationship between *HLA-B27* and ethnicity was detected (p=0.0024) primarily driven by a high prevalence of *HLA-B27* in subjects of white European descent, and a low prevalence in Hispanic subjects (Table II). The prevalence of *HLA-B27* varied significantly between centres even amongst axSpA cases of white European descent (herein termed 'white Europeans') (Table I). High *HLA-B27* prevalence (>70%) was reported in axSpA cases of white European descent by centres 1, 7, 24 and 34: Centre 1, 20/23 (87%); Centre 7, 7/9 (78%); Centre 24, 5/7 (71%); Centre 34, 3/3 (100%). In contrast, Centres 35 (11/27, 41%) and 12 (7/14, 50%) reported lower *HLA-B27* carriage amongst cases with the same ethnicity.

Analyses using genetic covariates

The predictive accuracy of genetic data was tested using genotypes from the Immunochip, an Illumina SNP microarray containing ~200,000 SNPs selected for studies of immune mediated diseases, including AS (11). The SNPs genotyped include 31 markers representing known AS GWAS associations (12, 13) (Supplementary Table II). To test the performance of these known

genetic covariates in a homogenous cohort we used 13,866 European samples from the IGAS Immunochip project (9,638 controls and 4,428 AS cases) that did not include the samples in the ASAS back pain cohort. These AS cases were 85% *HLA-B27* positive.

We investigated the discriminatory capacity of the 31 known AS-associated SNPs as well as *HLA-B27* (Table III) for the presence or absence of AS in a logistic regression model using 20-fold cross-validation in the whole sample set. The AS-associated SNPs were able to predict the AS affection status with an AUC of 0.91±0.01 (standard deviations). In contrast, considering the subset of cases in the ASAS back pain cohort meeting the ASAS imaging criteria (which do not require the carriage of *HLA-B27*) in comparison with the IGAS controls, the AUC was somewhat lower (0.83±0.05), indicating that the ASAS imaging positive cases are less well captured by established AS genetic associations than are the IGAS cases (Table III). This was similar to a comparison of all ASAS positive *versus* ASAS negative cases (0.84±0.04). This was supported by the presence of significant genetic differences comparing IGAS AS and ASAS imaging positive cases directly (AUC 0.67±0.05). A significant excess carriage of AS-associated SNPs in the ASAS imaging negative controls was seen relative to the IGAS controls (AUC 0.68±0.06) suggesting a lower specificity of classification amongst the ASAS criteria subjects.

Table II. Ethnicity and HLA-B27 status in the overall ASAS cohort.

Ethnicity	AxSpA +		AxSpA-		
	HLA-B27 pos (n)	HLA-B27 neg (n)	HLA-B27 pos (n)	HLA-B27 neg (n)	% HLA-B27 pos
Asian	**28**	**24**	**0**	**34**	**33%**
African	0	3	0	2	0%
East Indian	1	0	0	1	50%
Hispanic	**6**	**8**	**0**	**12**	**23%**
Indigenous	0	1	0	0	0%
Mixed	2	2	0	0	50%
Combined white Europeans	**56**	**31**	**31**	**41**	**55%**

Table III. Receiver-operator curve for comparisons involving IGAS AS case-control and ASAS study cohorts. Values are reported ± standard deviation.

Case set	'Control' set	ROC AUC
IGAS AS	IGAS controls	0.9 ± 0.01
IGAS AS	TOTAL ASAS Controls	0.90 ± 0.03
IGAS AS	ASAS Imaging Pos Cases	0.67 ± 0.05
IGAS AS	ASAS Imaging Neg Controls	0.87 ± 0.03
Overall ASAS Positive	Overall ASAS negative	0.84 ± 0.04
ASAS Imaging Pos cases	IGAS controls	0.83 ± 0.05
ASAS Imaging Pos cases	TOTAL ASAS Controls	0.78 ± 0.06
ASAS Imaging Pos cases	ASAS Imaging Neg Controls	0.65 ± 0.06
ASAS Imaging Neg controls	IGAS controls	0.68 ± 0.04

Discussion

The aim of this study was to test whether genetic profiling could be used to identify axSpA or AS patients, particularly in a heterogeneous sample set. To date, most genetic studies in AS have been conducted in homogeneous tightly-defined cohorts with the aim of identifying genetic associations rather than developing diagnostic tests for use in clinical settings. However, an important potential application of genetic profiling is in early diagnosis or prediction of disease. For such a utility the test must be robust enough to cope with samples from ethnically diverse patients and heterogeneous disease presentation. Our findings suggest that whereas genetic profiling works well in a research cohort defined by the mNY classification criteria, in the more diverse ASAS back-pain cohort, reflecting daily experience in a rheumatology practice, genetic profiling is less discriminatory.

In addition to ethnic diversity, the genetic variety of the ASAS cohort is further confounded by the heterogeneous nature of SpA. Some but not all nr-axSpA patients will progress to AS (14), so it is likely that nr-axSpA is genetically more heterogeneous than AS (9, 15-17). This heterogeneity is supported by the stronger discriminatory ability of AS-associated genes to identify AS patients in the IGAS than the ASAS cohorts.

Of note, 43% of the entire ASAS cohort were positive for *HLA-B27* prior to the clinical diagnosis of the ASAS rheumatologist as SpA or no SpA, although the exact percentage varied substantially between centres even amongst the same ethnic group. This high *HLA-B27* prevalence suggests that low back pain patients were selectively referred into the ASAS study because the referring physician considered axSpA was a likely diagnosis. This circumstance must inevitably lead to enrichment of SpA related risk genes including *HLA-B27* not only in SpA patients but also in patients not meeting the ASAS axSpA criteria. These factors would negatively affect the performance of genetic profiling in such a study. Interestingly, we note that amongst the white European AS cases in the ASAS cohort, only 68% were *HLA-B27* carriers, as might be expected for axial SpA cohorts, but rather lower than the expected 80%-90% for AS. The differences in *HLA-B27* carriage between centres were considerable and suggest ascertainment differences which might contribute to the lower than expected *HLA-B27* carriage. For example, in samples designated of Han Chinese origin in Centre 14, 15/35 (44%) of axSpA cases were *HLA-B27* carriers while Centre 17 from the same region reported 11/11 (100%) of axSpA cases as *HLA-B27* carriers (comparing *HLA-B27* carriage between centres, p=0.00085).

This further supports that the IGAS Immunochip cases are a much more homogenous group in terms of their underlying genetic risk for AS than are the cases in the ASAS axSpA cohort. The ROC analysis comparing the IGAS

controls and ASAS imaging negative (but enriched for borderline cases with the presence of some clinical SpA features including *HLA-B27*) subjects shows that the imaging negative subjects carry an excess of AS-associated genes compared with true negative controls. This is consistent with the fact that the ASAS criteria are not 100% sensitive (reported sensitivity imaging arm 66%), and it is possible that some of these cases will go on to develop disease that meets the ASAS criteria. The ROC analysis of the overall ASAS positive vs negative groups had an AUC of 0.84. This analysis is affected by the inclusion of the clinical arm, where the cases are required to be HLA-B27-positive, elevating the sensitivity of genetic testing and the AUC. Further, the excess of HLA-B27 positive subjects in the controls, likely caused by its use to ascertain cases in the ASAS study, will have reduced the specificity of genetic testing, as well as the AUC. Thus in this analysis combining the ASAS imaging and clinical classification criteria, the AUC, sensitivity and specificity reflect both the requirement for carriage of HLA-B27 in the clinical criteria, and the performance of the ASAS criteria in differentiating those that have axial SpA from those that have other causes of their back pain

Designing criteria which are both highly sensitive and specific is particularly challenging, especially where the 'gold standard' for diagnosis, in the case of the ASAS criteria - as well as in many other criteria - the physician's diagnosis, is to some extent itself subjective, and based on levels of suspicion of disease dependent on clinical presentation, pathology results and imaging, and where early on in disease in particular, the clinical manifestations are diverse and frequently incomplete. An alternative explanation for the enrichment of AS associated genes in axSpA negative cases not fulfilling the ASAS criteria is the fact that AS associated genes are found in subjects that never develop axial SpA. Yet certain disease manifestations, such as inflammatory back pain or response to NSAIDs, which are never 100% specific may occur in individuals with back pain and may lead to rheumatology referral (as in the ASAS cohort), but were not sufficient after an extensive diagnostic work-up for labelling as axial SpA, either by clinical diagnosis nor by the ASAS classification criteria.

We conclude that, that genetic profiling in a "real-world" cohort has limited power for early disease diagnosis in nr-axSpA diagnosed by the ASAS axSpA classification criteria, with both ethnic and disease heterogeneity confounding the contribution of AS-associated genes to disease development.

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