Polygenic Risk Scores have high diagnostic capacity in ankylosing spondylitis


ABSTRACT

Objective We sought to test the hypothesis that Polygenic Risk Scores (PRSs) have strong capacity to discriminate cases of ankylosing spondylitis (AS) from healthy controls and individuals in the community with chronic back pain.

Methods PRSs were developed and validated in individuals of European and East Asian ethnicity, using data from genome-wide association studies in 15 585 AS cases and 20 452 controls. The discriminatory values of PRSs in these populations were compared with other widely used diagnostic tests, including C-reactive protein (CRP), HLA-B27 and sacroiliac MRI.

Results In people of European descent, PRS had high discriminatory capacity with area under the curve (AUC) in receiver operator characteristic analysis of 0.924. This was significantly better than for HLA-B27 testing alone (AUC = 0.869), MRI (AUC = 0.885) or C-reactive protein (AUC = 0.700). PRS developed and validated in individuals of East Asian descent performed similarly (AUC = 0.948). Assuming a prior probability of AS of 10% such as in patients with chronic back pain under 45 years of age, compared with HLA-B27 testing alone, PRS provides higher positive values for 35% of patients and negative predictive values for 67.5% of patients. For PRS, in people of European descent, the maximum positive predictive value was 78.2% and negative predictive value was 100%, whereas for HLA-B27, these values were 51.9% and 97.9%, respectively.

Conclusions PRS have higher discriminatory capacity for AS than CRP, sacroiliac MRI or HLA-B27 status alone. For optimal performance, PRS should be developed for use in the specific ethnic groups to which they are to be applied.

INTRODUCTION

Ankylosing spondylitis (AS) affects approximately 0.2%–0.6% of individuals of European descent and Chinese. Early treatment with biologic therapies in those with more severe forms of the disease achieves more effective clinical responses and probably reduces the rate joint fusion in the long term. However, other causes of chronic back pain are common in the community, and AS is responsible for only a minority of these cases. It can be difficult to distinguish AS from other causes of back pain, particularly early in the disease with the consequence that the diagnosis of AS is often significantly delayed; many surveys undertaken in a variety of different health systems suggest an average delay of 6–10 years. A recent North American survey reported that fewer than half (37.1%) of patients with AS reported that they were correctly diagnosed within 1 year of seeking medical attention, and 32.8% waited more than a decade to receive the diagnosis. Population surveys suggest that as many as 80% of cases in the community remain
Spondyloarthritis

undiagnosed and therefore may not receive appropriate effective treatment. There is thus a great need for improved testing to improve early accurate diagnosis.

Currently, the most widely used tests for AS in those with chronic back pain are measurements of acute phase reactants, such as erythrocyte sedimentation rate and C-reactive protein (CRP), genetic testing for HLA-B27 and imaging—either plain radiographs or MRI of the sacroiliac joints. However, each of these tests has limitations. In brief, acute phase reactants and MRI are only positive after disease develops and are therefore not useful for predicting disease risk. Acute phase reactants have only moderate sensitivity and specificity, particularly in early disease. MRI is expensive and is not universally available. Genetic factors are the major determinants of the risk of developing AS, with heritability assessed in twins of >90%. Although HLA-B27 alone contributes 20% of the variation in disease risk, the remainder of the genetic risk is determined by thousands of common genetic variants, each of which has only a very small effect. Polygenic Risk Scores (PRS) use combinations of hundreds to thousands of genetic variants to quantify an individual’s genetic risk of disease. Unlike HLA-B27 testing which is categorical or dichotomous in outcome, PRS are continuous measures. They are of particularly strong predictive value for low-frequency diseases with high heritability, such as AS. Here, we describe the development and validation of PRS for AS in two different ethnic groups and compare its performance to standard screening or diagnostic tests.

METHODS

Study population

AS was defined according to the modified New York criteria. Following genotyping quality control, there were 8244 cases and 14 274 controls of western European descent; 6001 cases and 4493 controls of East Asian (Chinese) descent; and 1340 cases and 1685 controls of Turkish and Iranian origin, respectively. Written informed consent was obtained from all cases, with approval from the relevant research ethics authorities at each participating centre. Cohort details are provided in online supplemental table S1.

Genetic data

Samples were genotyped using the Illumina Core-Exome SNP genotyping microarray, according to the manufacturer’s recommendations (chip versions used per cohort are provided in online supplemental table S1). Bead intensity data were processed and normalised for each sample, and genotypes called, using GenomeStudio V2.0 software (GenomeStudio Software Downloads (illumina.com)). Standard quality control measures as outlined in the Supplementary Methods were applied including identification and exclusion of cryptic-related samples, exclusion of samples with an outlying heterozygosity rate (3 SD from the mean in each cohort) or excess missingness (>5%). Single nucleotide polymorphisms (SNPs) with genotyping missing rate >2%, p value of Hardy-Weinberg equilibrium test <1×10^{-6}, or with allele frequency <1% were removed. Population stratification was accessed using Shellfish (http://www.stats.ox.ac.uk/~davison/software/shellfish/shellfish.php). PRS analyses were performed with and without inclusion of principal components and gender as covariates. Results including principal components and gender as covariates are reported in online supplemental table S2 and are very similar to the results not including these covariates.

HLA-B27 imputation was performed using SNP2HLA, using a deep sequencing Chinese reference panel (n=10 689) for East Asian samples and Type 1 Diabetes Genetics Consortium (n=5225) panel of combined HLA types and MHC SNP genotypes for all other subjects.

PRS were calculated for each individual using the adaptive MultiBLUP algorithm (implemented in the software LDAK V5.0). LDAK first divides the genetic data into chunks of size 75 000 bp and then performs association test for all the chunks and thinned out SNPs in strong linkage disequilibrium. The significant chunks with p value <1×10^{-5} and all adjacent chunks with p value <0.01 are merged into regions. Then the variance components and effect size of SNPs are estimated, and the effect size of the SNPs used to calculate the PRS. A 10-fold cross-validation analysis was performed as internal validation; a separate external validation was performed in the British and North American subjects, as well as through comparison of performance of PRS trained in either European descent or East Asian subjects, then validated in a separate ethnic group. In regard to cross-validation studies, the case–control cohort being studied is divided into 10 equal folds randomly with same case–control ratio. Nine folds of samples were used as a training set and the remaining fold of samples was retained as the validation data for testing the model generated by the training set. The process was repeated 10 times, with each of the 10-folds used only once as the validation data. The out-of-fold predictions based on the effect sizes of the selected SNPs were obtained for the test fold. All the predictions of 10 test folds were merged, after which statistical analysis was performed using all out-of-fold test set predictions to maximise sample size for internal testing. The resulting weighted predictors were then applied to the test cohort to obtain per sample scores from which the area under the curve (AUC) was obtained using receiver operator characteristic (ROC) analysis. R package pROC was used to calculate the 95% CI of the AUC and also compare AUCs from two models. Positive (PPV) and negative predictive values (NPV) were then calculated for PRS centroids, assuming different prior probabilities of AS. The continuous net reclassification improvement (NRI), a statistic that aims to quantify differences in classification performance of different models, was calculated using the R package PredictABEL and used to compare accuracy of diagnostic assignment by HLA-B27 testing and PRS.

RESULTS

ROC analyses of test discriminatory capacity are summarised in table 1. In 10-fold cross-validation in this case–control cohort, the PRS had AUC of 0.924 (95% CI 0.920 to 0.928) (figure 1). The AUC of HLA-B27 testing alone was 0.869 (95% CI 0.865 to 0.874), which was statistically significantly less discriminatory than the PRS (p=2.2×10^{-16}). Additionally, the NRI was positive (0.717, 95%CI 0.692 to 0.743), confirming that the PRS is an improvement on HLA-B27 alone. A PRS including only non-MHC SNPs performed less well (AUC 0.782), as did a PRS including only 103 (genotyped or imputed) loci previously reported to have achieved genome-wide significance in AS (AUC=0.659). MRI has a reported sensitivity of 85% and specificity of 92% in AS, which correlates with an AUC of 0.885. CRP has a reported sensitivity of 50% and specificity of 80% for the disease (AUC=0.7).

To test the performance of the PRS using external validation, the European descent cases were divided into British and North American cohorts, and controls divided in the same proportion as the two case cohorts. PRS was then

---


---
Spondyloarthritis developed in the British training set (n=6499 cases, 12163 controls) and externally validated in the North American case–control cohort (n=1128 cases, 2111 controls). The PRS in the North American cohort had AUC of 0.928 (95% CI 0.918 to 0.939), significantly higher than HLA-B27 alone (0.895, 95% CI 0.883 to 0.906, p=1.73×10⁻⁵) (online supplemental figure S1). These findings are very similar to the cross-validation analysis of the overall dataset reported above.

The PRS developed in all the European descent subjects, with 3994 SNPs (including 2244 major histocompatibility complex (MHC) SNPs), had moderate discriminatory capacity in East Asian, Iranian and Turkish cases and controls (AUC=0.788, 0.852 and 0.854, respectively), better than the performance of HLA-B27 alone in the Iranian and Turkish cohorts, but not in East Asians. In contrast, the PRS developed in East Asian subjects, then tested by cross-validation (i.e. also in East Asian subjects), had much better discriminatory capacity (AUC=0.948, 95% CI 0.943 to 0.952) than did the PRS developed in European descent subjects when tested in East Asian subjects. The PRS involving 8659 SNPs (including 2417 MHC SNPs) developed with all the East Asian subjects also performed well in European descent subjects (AUC=0.880, online supplemental figure S2), better than the discriminatory performance of HLA-B27 in each of the other three populations tested.

In clinical practice, the utility of all such tests depends on the prior probability of the disease concerned. The PPV and NPV of the PRS and HLA-B27 in European subjects are presented in figure 2 in the setting of a patient under 45 years of age, attending a physician with a history of back pain for 3 months or more. Published studies report that in this setting the prior probability of AS is ~30%,²⁴–²⁶ but as this may vary according to referral patterns, we have additionally provided findings for prior probabilities of 10% and 20% (online supplemental figures S5 and S6; East Asian specific findings are presented in online supplemental figures S7–S9).

### Table 1 ROC analysis findings (AUC) of genetic risk scores in different populations

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Population tested in</th>
<th>European</th>
<th>East Asian</th>
<th>Iranian</th>
<th>Turkish</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B27 alone</td>
<td></td>
<td>0.869 (0.865–0.874)</td>
<td>0.901 (0.895–0.906)</td>
<td>0.831 (0.807–0.854)</td>
<td>0.821 (0.804–0.838)</td>
</tr>
<tr>
<td>European non-MHC PRS</td>
<td></td>
<td>0.782 (0.776–0.788)</td>
<td>0.594 (0.539–0.600)</td>
<td>0.534 (0.500–0.569)</td>
<td>0.568 (0.542–0.595)</td>
</tr>
<tr>
<td>European overall PRS</td>
<td></td>
<td>0.924 (0.920–0.928)*</td>
<td>0.788 (0.779–0.796)</td>
<td>0.852 (0.826–0.879)</td>
<td>0.854 (0.836–0.872)</td>
</tr>
<tr>
<td>East Asian non-MHC PRS</td>
<td></td>
<td>0.555 (0.547–0.563)</td>
<td>0.731 (0.722–0.741)*</td>
<td>0.565 (0.531–0.598)</td>
<td>0.554 (0.528–0.581)</td>
</tr>
<tr>
<td>East Asian overall PRS</td>
<td></td>
<td>0.880 (0.875–0.887)</td>
<td>0.948 (0.943–0.952)*</td>
<td>0.872 (0.848–0.895)</td>
<td>0.840 (0.821–0.860)</td>
</tr>
<tr>
<td>MRI EUR</td>
<td></td>
<td>0.885</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI CH⁴¹</td>
<td></td>
<td>0.62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*10-fold cross-validation. All other PRS AUC values are external validation statistics. AUC, area under the curve; CRP, C-reactive protein; PRS, Polygenic Risk Score; ROC, receiver operator characteristic.
an HLA-B27 test will be positive in 31% of those tested with a PPV of 80.6%, and in the 69% of those with a negative test, the NPV is 92.4%. Using the PRS, the PPV is >80.6% for top 35% of those screened, and achieves a higher maximum value (93.3%) than does HLA-B27 (80.6%) (figure 2). The PRS NPV will be >92.4% for 65% of those screened, and also achieves a higher maximum value (99.6%) than does HLA-B27 (92.4%). Considering the situation where only 10% of screened patients have AS, then HLA-B27 will be positive in 16% of those tested. In this group, HLA-B27 positivity has a PPV of 51.9%, and a negative result (seen in 84% of screened patients) has an NPV of 97.9%. Using the PRS, the PPV is >51.9% for 35% of patients and has a much higher maximum value (78.2% vs 51.9%). The NPV for the PRS is >97.9% for 65% of patients and achieves a slightly higher maximum value than HLA-B27 testing (100% vs 97.9%).

Considering general population screening, at least 8% of the European population carry HLA-B27,27 yet only 5% of carriers of this allele will develop AS28; as such, no higher PPV can be achieved using HLA-B27 testing alone. In contrast, for the PRS, the PPV for the top 8% of the population is three times higher (15.1%), and it is higher than 5% for the top 35% of the population. The NPV for HLA-B27-negative status is 99.9%, which is exceeded by the PRS for 62.5% of the population.

**DISCUSSION**

Distinguishing AS from other causes of chronic back pain remains an important issue in rheumatology. HLA-B27 testing can have a valuable PPV for AS, particularly in clinical settings where the pretest probability of the disease is relatively high compared with the general population. It is therefore included in the Assessment of Spondyloarthritis International Study Group (ASAS) axial spondyloarthritis (axSpA) classification criteria and is an essential criterion for those with no available imaging evidence of disease. HLA-B27 testing has also been recommended for screening patients with chronic back pain to identify those at higher risk of AS or the related group of diseases axSpA, for referral to specialist services.23 25 However, HLA-B27 only contributes ~20% of the overall heritability of AS, which is estimated to be ≥90% overall, indicating a substantial non-MHC component.29 This suggests that PRS, which capture the common-variant component of heritability, are likely to be much more informative than HLA-B27 tests alone. Our study confirms this, with the PRS performing better than HLA-B27 testing in both AUC and continuous NRI analyses, irrespective of the prevalence of AS among those being tested. We confirm these findings both by internal cross-validation and by external validation. For 35% of the population, the PPV is higher for the PRS than for HLA-B27 testing, and the NPV is higher for >65%. In particular, the peak PPV is substantially higher for the PRS than for HLA-B27 and is informative for a far higher proportion of patients, as it is a continuous variable whereas HLA-B27 is dichotomous. PRS testing also has higher discriminatory capacity for AS than MRI, and far higher than CRP. Accurate interpretation of MRI scans is known to be dependent on training and experience, and particularly in inexperienced, untrained hands may perform worse than the average reported performance, in which setting PRS may be particularly valuable.

Chronic back pain of >3 months’ duration has previously been shown to have very low heritability attributable to common genetic variants (minor allele frequency >0.01) such as those included in our AS PRS (common variant heritability = 6.43%30–7.6%31) and not to be genetically correlated with AS. Therefore, it is unlikely that the AS
PRS will prove less discriminatory in practice in the clinical setting of patients presenting with chronic back pain than the estimates presented here. A limitation of this study is that the performance of the PRS has not been formally tested in this setting, where it will require further evaluation.

axSpA refers to a spectrum of diseases. Patients with radiographic sacroiliitis are classified as having AS, whereas those without X-ray changes are classified as having non-radiographic (nr)-axSpA. The current PRS may have prognostic value in distinguishing the 16%–24% of nr-axSpA cases that are likely to go on to develop AS. Whether the PRS we report here will prove more informative than HLA-B27 testing alone in patients with nr-axSpA itself is unknown. The ASAS have previously demonstrated that patients meeting the ASAS classification criteria for axSpA who do not yet have AS have a much lower average genetic risk score than patients with AS, using only genome-wide significant AS loci. Whether this is because nr-axSpA is actually genetically distinct from AS, or reflects the greater clinical and likely aetiopathogenic heterogeneity of nr-axSpA, will require further study.

As with the use of PRS in the screening of individuals with chronic back pain, its performance in nr-axSpA will also require further study. Similarly, the performance of the PRS in males compared with females, in subjects with environmental risk factors for the disease such as cigarette smoking, and in subsets of patients such as those with extraskeletal manifestations of AS requires further study. In that regard, the excellent performance of a PRS in patients with acute anterior uveitis complicating AS (AUC=0.96; 95% CI 0.955 to 0.966) suggests that at least in some AS subsets the performance of the PRS will be even better than reported here.

PRS testing can be performed using data from any dense SNP microarray. Indeed, the performance of the PRS reported here was high despite our use of a relatively low density SNP microarray—the Illumina Core-Exome chip (>520,000 variants, including many rare and non-polymorphic variants that do not contribute to the PRS). The performance of PRS testing would be likely to improve further with use of microarrays with better SNP coverage, or with whole genome sequencing. It has been estimated that up to 12 million Americans have had SNP microarray testing performed by commercial services such as 23andMe and Ancestry. At little additional cost, these data would probably prove suitable for the calculation of the AS PRS we report, as well as enabling PRS for many other diseases in which they have been shown to be informative. The cost-effectiveness of the PRS we report here needs to be confirmed in further studies. As the genetic profile of AS becomes better understood, the discriminatory capacity of these tests is also likely to increase. For example, it is likely that many of the SNPs included in the PRS at present are not truly associated with AS, but just add noise to the test.

As there is no preventive therapy yet for AS, general population screening to identify patients at high risk of the disease is not recommended except, perhaps, for those at increased risk, such as the relatives of those with AS (given the high sibling recurrence risk of 8.2%). PRS performs significantly better than HLA-B27 testing alone in the general population, with the PPV of the −8% of the general population who carry HLA-B27 being 5%, compared with the peak PPV of the PRS of 15.1%. Similarly, the NPV for the PRS exceeds that of HLA-B27 testing for most of the population. Although the PPV for PRS testing for general population screening is modest, the test performs well compared with other widely used screening tests. For example, the PPVs for 10-year risk of coronary heart disease of a high total cholesterol (≥240 mg/dL)—a threshold above which many patients will be prescribed cholesterol-lowering therapy—are 10.3% in women and 18.6% in men, similar to the top 20% of PPVs of PRS for AS in general population screening. Among those who have already had SNP microarray testing performed, knowledge of a high AS-PRS even in the absence of symptoms may heighten clinician awareness of the possible diagnosis, reduce delay and assist with earlier appropriate and effective treatment, given the current long diagnostic delays.

Our study shows that the performance of the PRS varies between ethnic groups, although it remains moderately high even when a PRS developed in subjects of (western) European descent is tested in eastern European/west Asian subjects such as Turks and Iranians. The PRS developed specifically for East Asians performed far better in that population than did the European PRS, indicating that at least for populations that are remotely related, ethnic-specific PRSs are preferable.

We conclude that PRS testing for AS has greater discriminatory capacity than HLA-B27 testing, MRI scanning or CRP testing, either alone or in combination. PRS could be used to screen patients with chronic back pain to identify subjects at increased risk of the disease for referral to secondary care and to assist in diagnosing the condition.

Author affiliations
Queensland University of Technology, Centre for Genomics and Personalised Health, School of Biomedical Sciences, Faculty of Health, Translational Research Institute, Woolloongabba, Queensland, Australia
Department of Rheumatology and Immunology, Shanghai Changzheng Hospital, Second Military Medical University, Shanghai, Shanghai, China
Australian Translational Genomics Centre, Queensland University of Technology (QUT), Translational Research Institute, Woolloongabba, Queensland, Australia
Department of Internal Medicine, Division of Rheumatology, School of Medicine, Manisa Celal Bayar University, Manisa, Turkey
UMR 1173, Inserm, Université de Versailles Saint-Quentin, Montigny-le-Bretonneux, France
Service de Rhumatologie, Hôpital Ambroise Paré, Assistance Publique-Hôpitaux de Paris, Boulogne-Billancourt, France
Laboratoire d’Excellence Inflamex, Université Paris Diderot, Sorbonne Paris Cité, Paris, France
Epidemiology Group, Institute of Applied Health Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Foresterhill, Aberdeen, UK
Aberdeen Centre for Arthritis and Musculoskeletal Health, University of Aberdeen, Foresterhill, Aberdeen, UK
Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran (the Islamic Republic of)
NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK
Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
Division of Allergy, Immunology, Rheumatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
School of Medicine, National Yang-Ming University, Taipei, Taiwan
Department of Medicine, University of Otago Wellington, Wellington, New Zealand
Department of Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand
Hanyang University Hospital for Rheumatic Diseases, Hanyang University, Seoul, Korea (the Republic of)
University of Queensland Diamantina Institute, University of Queensland, Brisbane, Queensland, Australia
Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan
Department of Medicine, Chung Shan Medical University, Taichung, Taiwan
Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan
QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia
Queensland Brain Institute, University of Queensland, Brisbane, Queensland, Australia
Population & Data Sciences, University of Texas Southwestern Medical Center, Dallas, Texas, USA
State Key Laboratory of Optometry, Ophthalmology, and Vision Science, Affiliated Eye Hospital Wenzhou Medical University, Wenzhou, Zhejiang, China
Institute for Glycomics, Griffith University, Nathan, Queensland, Australia
Center for Precision Medicine, First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China


Spondyloarthritis

20.Institute of Life Sciences, Wenzhou University, Wenzhou, Zhejiang, China
21.Rheumatology Department, First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China
22.BeiJing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology & Visual Sciences Key Lab, Beijing, Beijing, China
23.Department of Medicine/Rheumatology, Cedars-Sinai Medical Center, Los Angeles, California, USA
24.Division of Medicine/Rheumatology, University of California San Francisco, San Francisco, California, USA
25.Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA
26.International Rheumatology, The University of Texas Health Science Center at Houston John P. and Katherine G. McGovern Medical School, Houston, Texas, USA
27.Department of Internal Medicine, Division of Rheumatology, McGovern Medical School at the University of Texas Health Science Center, Houston, Texas, USA
28.NIHR Oxford Musculoskeletal Biomedical Research Unit, Botnar Research Centre, University of Oxford, Oxford, UK
29.School of Clinical Medicine, Tsinghua University, Beijing, China
30.Beijing-Tsinghua Center for Life Sciences, Tsinghua University, Beijing, China
31.NIHR Biomedical Research Centre at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London, London, UK
32.Twitter Nurulh Adrian @nurulh Adrian, Gary J Macfarlane @UAberdeenEpi and Gareth T Jones @theraG_senol

Acknowledgements We would like to thank all participating subjects with ankylosing spondylitis and healthy individuals who provided the DNA and clinical information necessary for this study. The TASC study was funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) grants R01-052915 and R01-AR046208. Funding was also received from the University of Texas Health Science Center at Houston CTSU grant UL1R022418, Cedars-Sinai CQRS Grant MO1-R01-RR03255, Intramural Research Program, NIAMS/NH and Rebecca Cooper Foundation (Australia).


Contributors Study design was performed by ZL, WX, PL, MHW, LG, MMH, MWR, JDR, BWJ, PX and MAB. Case recruitment was performed by WX, NA, MA, MM, HMG, CTC, AHA, SS, GT1, SYB, GW, AJ, EF, LS, ML, JCCW, NM, MIW, MLI, YW, JZ,箬, BF, ZB, MW, LG, MSH, LQ, LW, DL, TNIK, JDR, BWJ, PX and MAB. Data analysis and/or interpretation were performed by ZL, WX, ML, PL, GW, EDG, LA, UX, XH and MAB. All authors were involved in completion of, and approved, the final manuscript.

Funding This study was funded, in part, by Arthritis Research UK (Grants 19536 and 18797), by the Wellcome Trust (grant number 076113) and by the Oxford Complementary Biomedical Research Centre ankylosing spondylitis chronic disease cohort (Theme Code: AS91202). XH is supported by the National Natural Science Foundation of China (Grant No. 31821003), National Key Research and Development Project (Grant No. 2018AAA10010300), Shanghai Municipal Key Clinical Specialty (shlszckbk20602), and Shanghai Science and Technology Development Funds (2020-SH-XY-Z). ZBJ was funded by a grant from the Zhejiang Provincial Natural Science Foundation of China (LD18H120011D). The New Zealand data were derived from participants in the Spondyloarthritis Genetics and the Environment Study (SAGE) and was funded by The Health Research Council of New Zealand. We acknowledge the Understanding Society; The UK Household Longitudinal Study. This is led by the Institute for Social and Economic Research at the University of Essex and funded by the Economic and Social Research Council. The survey was conducted by NatCen and the genome-wide scan data were analysed and deposited by the Wellcome Trust Sanger Institute. Information on how to access the data can be found on the Understanding Society website https://www.understandingsociety.ac.uk. This work was also supported by the National Institute for Health Research (NIHR) Leeds Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. French sample collection was performed by the Groupe Francais d’Etude Génétique des Spondyloarthritides, coordinated by Professor Maxime Breban and funded by the Agence Nationale de Recherche GEMISA grant reference ANR-10-MEDI-002. We acknowledge and thank the TCRI AS Group for their support in recruiting patients for the study (see below). The authors acknowledge the sharing of data and samples by the BSRBR-AS Register team in Aberdeen. Chief Investigator, Professor Gary Macfarlane and Dr Gareth Jones, Deputy Chief Investigator created the BSRBR-AS study which was commissioned by the British Society for Rheumatology, funded in part by Abbvie and the genome-wide scan data were externally peer reviewed. The QIMR control samples were from parents of adolescent twins collected in the context of the Brisbane Longitudinal Twin Study 1992–2016, support by grants from NHMRC (NGM) and ARC (MWR). We thank Anjali Henders, Lisa Bowdler, Tabatha Gonzales for biological collection and Kerrie McKinney and Scott Gordon for curating samples for this study. MAB is funded by a National Health and Medical Research Council (Australia) Senior Principal Research Fellowship (1024879), and support for this study was received from a National Health and Medical Research Council (Australia) program grant (566938) and project grant (569829), and from the Australian Cancer Research Foundation and Rebecca Cooper Medical Research Foundation. We are also very grateful for the invaluable support received from the National AnaKlyosing Spondylitis Society (UK) and Spondyloarthritis Association of America in case recruitment. Additional financial and technical support for patient recruitment was provided by the National Institute for Health Research Oxford Musculoskeletal Biomedical Research Unit and NIHR Thames Valley Comprehensive Local Research and an unrestricted educational grant from Abbott Laboratories. This research was financially supported by the National Institute for Health Research Biomedical Research Centre based at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London and/or the NIHR Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Written informed consent was obtained from all cases, with approval from the relevant research ethics authorities at each participating centre. The overall programme was reviewed and approved by Metro South Hospital Research Ethics Committee (approval reference HREC/05/QPAH/221).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Details of the polygenic risk scores will be made available depending on completion of data transfer agreements with King’s College London.
Supplemental material  This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access  This is an open access article distributed in accordance with the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Zhihu Li http://orcid.org/0000-0002-2924-9120
Nurulah Akkoc http://orcid.org/0000-0002-3718-171X
Maxime Breban http://orcid.org/0000-0002-6922-9395
Gary J MacFarlane http://orcid.org/0000-0003-2322-3314
Mahdi Mahmoudi http://orcid.org/0000-0002-8164-8831
Helena Marzo-Ortega http://orcid.org/0000-0002-9683-3407
Andrew A Harrington http://orcid.org/0000-0003-4372-3252
Simon Stebbings http://orcid.org/0000-0002-2824-4440
Gareth T Jones http://orcid.org/0000-0003-4071-3187
James Cheng-Chung Wei http://orcid.org/0000-0003-0310-7769
Minluee Lee http://orcid.org/0000-0002-4329-506X
Xiaobing Wang http://orcid.org/0000-0002-4302-2213
Zi-Bing Jin http://orcid.org/0000-0003-0515-698X
Michael M Ward http://orcid.org/0000-0003-1857-9367
Tae-Hwan Kim http://orcid.org/0000-0002-3542-2276
John D Revell http://orcid.org/0000-0001-5890-0913
Bryan Paul Wordsworth http://orcid.org/0000-0001-7512-3468
Huji Xu http://orcid.org/0000-0002-8588-118X
Matthew A Brown http://orcid.org/0000-0003-0538-8211

REFERENCES
Correction: Polygenic Risk Scores have high diagnostic capacity in ankylosing spondylitis


An error occurred in figure 1. The key for the figure has swapped the colours of the lines for ‘B27 status’ and ‘non-MHC GWS variants’. The numbers for these are given in the text but the figure is wrong and should be:

---

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.