Genetic association of non-MHC region with ankylosing spondylitis in a Chinese population

Ankylosing spondylitis (AS) is a chronic inflammatory disease mainly affecting the sacroiliac joints and spine. In order to examine overall genetic susceptibility of AS, several genome-wide association studies (GWASs) were performed in Caucasian populations, and a number of genetic polymorphisms in non-major histocompatibility complex (MHC) regions were found, such as ERAP1, IL23R as well as many others. However, only a small portion of the single nucleotide polymorphisms (SNPs) were validated in East Asian (EA) populations. In recent years, multiple studies indicated significant genetic differences between different European and EA populations. To resolve this further, we have examined all reported AS-associated SNPs in non-MHC regions in Chinese patients with AS. A total of 1289 patients with AS and 1536 controls were included in this analysis, which have not been included in prior analyses. The sociodemographic and clinical characteristics of the cohort are presented in online supplementary table S1.

In this study, the candidate SNPs were mainly selected from six GWAS studies published from 2007 to 2016. Overall, 69 SNPs in non-MHC regions were included, 32 of which had not been validated in EA population before. The results of six loci (rs6759298, rs2297518, rs7530164, rs12615545, rs5837881 and rs27044) were consistent with prior reports in the Caucasian populations (table 1). Among them, the SNP rs2297518 in the NOS2 gene (OR/p_value (false discovery rate (FDR))=1.328/8.6E-03) and rs5837881 in an intergenic region (OR/p_value (FDR)=0.80/0.04) were not validated previously in EA populations, whereas four other SNPs were consistent with previous reports in Asian cohorts. Nine loci that had been previously associated with AS in relatively small cohorts of Chinese population were not validated in the present results (online supplementary table S2). Twenty-four loci that previously showed an association with AS but with p value not at genome-wide significance (>10−8) in both Caucasian and EA populations were not validated in our results (online supplementary table S3). Thirty-one loci previously reported implicated only in Caucasians did not show an association with AS in this study (online supplementary table S4).

In this study, all six SNPs showed significant differentiation between AS and controls in both Caucasians and our samples. Among them, rs6759298 located in a ‘gene desert’ at chromosome 2p15 showed highest significance in both Caucasian and Chinese data (OR/p_value=1.31/3.60E-41, 1.22/3.81E-04, respectively). The Genotype-Tissue Expression dataset showed that rs6759298 has expression quantitative trait loci (eQTL) with B3GNT2 (online supplementary figure 1A). In addition, the database of Mouse Genome Informatics (MGI) showed that mice with B3gnt2-knocked-out showed increased levels of inflammatory cytokines such as interleukin (IL)-6, IL-1β and tumour necrosis factor-alpha. An association with another SNP (rs2297518) located in NOS2, which has never been reported in Chinese data of patients with AS, was found. It is a mutation that causes deleterious alterations in the coding region of NOS2. Rs7530164 is an intron variant on SULT1A2, which has eQTL with SULT1A1 expression (online supplementary figure 1B). MGI showed Sult1c1-knockout- mice have abnormal immune responses and increased sacral vertebrae number. Rs12615545 is nearUBE2E3 and has eQTL with UBE2E3 (ubiquitin enzyme)

Table 1 Genetic associations with AS and controls in the Chinese population

| Gene/region | SNP       | Allele | Western  | OR     | P values | Asian  | OR     | P values | This study | MAF | OR     | P values | P_adj |
|-------------|-----------|--------|----------|--------|----------|--------|--------|----------|-----------|------|--------|----------|-------|
| 2p15        | rs6759298 | G      | 1.31     | 3.60E-41 | 1.28     | 1.60E-06 | 0.4418 | 0.3917   | 1.22     | 3.81E-04 | 8.60E-03 |
| NOS2        | rs2297518 | A      | 1.13     | 6.30E-07 | 1.16     | 0.012   | 0.2920 | 0.2472   | 1.26     | 2.35E-04 | 8.60E-03 |
| SULT1A2     | rs7530164 | A      | 1.11     | 1.40E-07 | 0.83     | 8.50E-04 | 0.2959 | 0.3379   | 0.82     | 6.66E-04 | 0.01    |
| UBE2E3      | rs12615545| T      | 0.90     | 2.30E-07 | 0.83     | 8.50E-04 | 0.2959 | 0.3379   | 0.82     | 6.66E-04 | 0.01    |
| Chr2 indel  | rs5837881 | T      | 0.88     | 1.26E-13 | NA       | NA      | 0.1490 | 0.18     | 0.80     | 3.14E-03 | 0.04    |
| ERAP1       | rs27044   | C      | 0.71     | 1.00E-06 | 1.30     | 9.37E-07 | 0.4694 | 0.5046   | 0.86     | 4.70E-03 | 0.05    |

AS, ankylosing spondylitis; MAF, minor allele frequency.
in oesophageal mucosa, suggesting it might be related to inflammation status (online supplementary figure S1C).

Other loci were not validated in our samples such as IL12R, ANTXR2 and FCGR2A. We postulated that some different SNPs located in the same genes or genes in the same pathway can substitute for those loci in the Chinese population as has been observed with IL23R. Therefore, it is essential to find associated SNPs in different cohorts by sequencing or different chip analyses to extend our knowledge to the pathogenesis of AS.

In conclusion, we genotyped 69 previously reported non-MHC AS-associated SNPs in a different Chinese cohort and found that six loci showed significant differences between patients with AS and controls in both Caucasian and EA populations. Usually, several SNPs may have similar effect to the same gene. Therefore, in the future, we can perform functional study of genes controlled by several SNPs in the mouse.

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Contributors JW and HZ designed the project and wrote the manuscript. JL and WP collected data, performed genotyping and analysis and wrote the manuscript. YL and YM managed all samples. QZ, WW and CY provided the ankylosing spondylitis information status (online supplementary figure S1C).

In conclusion, we postulated that some different SNPs and information status (online supplementary figure S1C).

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REFERENCES

1 Brown MA, Kennedy LG, MacGregor AJ, et al. Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. Ann Rheum Dis 1997;46:823–8.
2 Wellcome Trust Case Control Consortium, Australo-Anglo-American Spondylitis Consortium (TASC), Burton PR, Australo-Anglo-American Spondylitis C, et al. Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. Nat Genet 2007;39:1329–37.
3 Davidson SI, Wu X, Liu Y, et al. Association of ERAP1, but not IL23R, with ankylosing spondylitis in a Han Chinese population. Arthritis Rheum 2009;60:3263–8.
4 Australo-Anglo-American Spondyloarthritis Consortium (TASC), Reveille JD, Sims AM, et al. Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci. Nat Genet 2010;42:123–7.
5 Choi CB, Kim TH, Jun JB, et al. ARTS1 polymorphisms are associated with ankylosing spondylitis in Koreans. Ann Rheum Dis 2010;69:582–4.
6 Evans DM, Spencer CC, Pointon JJ, et al. Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. Nat Genet 2011;43:761–7.
7 International Genetics of Ankylosing Spondylitis Consortium (IGAS), Cortes A, Hadler J, et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. Nat Genet 2013;45:730–8.
8 Karadere T, Keidel SM, Pointon JJ, et al. Ankylosing spondylitis is associated with the antrax toxin receptor 2 gene (ANTXR2). Ann Rheum Dis 2014;73:2054–8.
9 Ellinghaus D, Jostins L, Spain SL, et al. Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. Nat Genet 2016;48:S10–8.
10 Robinson PC, Leo PJ, Pointon JJ, et al. Exome-wide study of ankylosing spondylitis demonstrates additional shared genetic background with inflammatory bowel disease. NPJ Genom Med 2016;1:16008.